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Vol. 38 SEPTEMBER, 1955 No. 3

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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Vol. 38, No. 3, September, 1955. Surgery is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States, $14.00 a year; Canada, $14.50; Foreign, $15.50. Entered as Second-Class matter January 20, 1937, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in the U. S. A.

SURGERY

VOL. 38 SEPTEMBER, 1955 NO. 3

Original Communications

A LONG-TERM FOLLOW-UP OF 10,098 SPINAL ANESTHETICS

II. INCIDENCE AND ANALYSIS OF MINOR SENSORY NEUROLOGICAL DEFECTS

LEROY D. VANDAM, M.D.,* AND ROBERT D. DRIPPS, M.D., PHILADELPHIA, PA.

(From the Department of Anesthesiology, Hospital of the University of Pennsylvania)

IN THIS series of papers concerning "A Long-Term Study of Neurological Complications of Spinal Anesthesia," the fact that major neurological sequelae had not been found provided the subject matter of the first report.[1] A number of lesser complications were discovered and these will be presented in the papers to follow. This report deals with the incidence of, and the factors contributing to, the development of minor sensory neurological defects after spinal anesthesia.

MATERIAL

During the years 1948 to 1951, a total of 8,460 persons given 10,098 spinal anesthetics at the Hospital of the University of Pennsylvania and elsewhere provided the opportunity to answer some of the unknown facts of neurological disease related to this technique of anesthesia. These patients, for whom this type of anesthesia had been carefully chosen and where every detail of the administration of the spinal anesthetic had been recorded, were interviewed in the immediate postoperative period and followed subsequent to their departure from the hospital. In this manner, accurate information of about 86 per cent or 8,699 of the total number of anesthetics was obtained for at least six months after anesthesia. In some, the follow-up period exceeded five years. If those who died subsequent to the operation are counted, the percentage of the total number of anesthetics for which information was available totals 89 per cent. The deaths were related in no way to the spinal anesthetic. A parallel study was conducted in 1,000 patients given general anesthesia for the same type of

This study was supported in part by Contract DA-49-007-md-475, Office of the Surgeon General, U. S. Army.

Received for publication Dec. 27, 1954.

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operations as were performed under spinal anesthesia to discover those symptoms and signs which might be common to the type of patient or to the operation performed.

GENERAL DESCRIPTION

There were 71 cases in which subjective or both subjective and objective evidences of neurological disease were recorded. In the control series of general anesthetics, similar complaints were not encountered. The subjective complaints were those of numbness, of numbness and tingling, of heaviness or burning, and some of these were associated with objective signs of neurological defect. These symptoms and signs were usually present in the immediate postoperative period and lasted from a few days to more than six months without progression in severity or extent. It is significant, perhaps, that the great majority of these complaints were confined to the lumbar and sacral areas of the body. There were a few persons who had tingling of the fingers without objective change, but these were thought to be of little significance. In 85 others, or 1.0 per cent of the total number of patients, symptoms were reported which, for want of a better term, we have called "irritative." These were complaints of cramps, of twisting, pulling, or drawing sensations in the lower extremities arising and subsiding in the first few days after operation. Since 0.9 per cent of the patients given general anesthesia had identical symptoms, we believe that they are not peculiar to spinal anesthesia and have therefore not included irritative complaints in this report.

Numbness in the Toes and Feet.—Five women and one man had numbness or tingling in the toes or feet. Pontocaine hydrochloride with glucose or glucose and epinephrine was the anesthetic used in all of these cases. Lumbar puncture was performed below the third lumbar intervertebral space with a No. 22 or No. 24 gauge needle in each instance. Though more than one puncture was made in two cases, neither paresthesias nor blood-stained cerebrospinal fluid were observed. The anesthetic levels attained ranged from the eleventh to the third thoracic dermatomes. Objective neurological findings were lacking in all, but the symptoms lasted up to six months in two cases. It may be pertinent that two of the patients had undergone vaginal delivery with the legs suspended in stirrups. A third patient had an inguinal herniorrhaphy.

Perineal Numbness.—Four men and two women complained of numbness at the base of the spine or in the buttocks. Four of the patients were given Pontocaine hydrochloride with glucose, none with epinephrine. Lumbar puncture was performed below the third intervertebral space in every case—with one insertion of the needle and the appearance of clear fluid. The only patient to experience a paresthesia, that in the left leg, subsequently had a numb feeling in the left buttock. Objective signs of numbness were found in two persons: one, an individual who had had an appendicectomy, and the other, a patient with a hemorrhoidectomy. There were no other neurological findings and the numbness lasted two months and six months, respectively. Three of the six

patients had had their legs suspended in stirrups, one for a vaginal delivery and episiotomy, another for a hemorrhoidectomy, and the third for a suprapubic prostatectomy.

Leg Numbness With and Without Pain.—Twenty patients, thirteen women and seven men, had numbness with or without pain in the legs. Pontocaine hydrochloride with glucose in twelve, and Pontocaine hydrochloride with glucose and epinephrine in four, were the anesthetics commonly used. A 16 gauge needle for a continuous catheter spinal anesthetic was used in one case and a 22 gauge or 24 gauge needle in all others. Two insertions of the needle were made in seven cases and multiple punctures in one. The subarachnoid space was entered only once in each case. Paresthesias produced in four cases at the time of lumbar puncture bore no relation to the eventual site of numbness. Sensory anesthetic levels up to the third dermatome were obtained. The legs were suspended in stirrups during the operation in eight instances. Operations were performed on the legs in two cases. In none of these 20 cases was antecedent neurological disease present, and in none could objective signs of neurological disease be found. The complaints indicated no progression of disease although they had lasted up to six months in some instances. The statement of one patient indicates how psychologic factors may play a role in these elicited reactions to spinal anesthesia. This woman wrote, "I had always feared that I would be unable to walk after spinal anesthesia."

Numbness Without Pain in the Thighs.—Twenty persons, ten men and ten women, had numbness localized mainly in one thigh. Pontocaine hydrochloride with glucose was the anesthetic given in 14 cases and Pontocaine hydrochloride with glucose and epinephrine in three. Lumbar puncture was performed with a 16 gauge needle for continuous catheter spinal anesthesia in five cases, with a 20 gauge needle in one case, and with a 22 gauge or 24 gauge needle in the remaining 14. More than one insertion of the needle was required in nine cases. Paresthesias to one leg were noted in seven cases and blood-stained cerebrospinal fluid was obtained in one. In three cases the subsequent appearance of numbness was on the same side where a paresthesia had been felt at the time of lumbar puncture. Spinal anesthesia was not satisfactory in one case and the levels of sensory anesthesia obtained in the others were as high as the third thoracic dermatome. Saphenous vein ligations were performed on two persons, an inguinal herniorrhaphy in one, and stirrups were used for the legs in four others. Four patients had been given two or more spinal anesthetics with the appearance of numbness after the first anesthetic in two cases and after subsequent anesthetics in the other two cases. One person had worn a truss for forty-two years and had complaints on that side after operation. A diabetic patient and a patient with syphilis, unsuspected preoperatively, given spinal anesthesia are included in this group. In only six of the 20 cases was objective evidence of diminished sensation found. The clear description provided by the other patients who were not examined strongly suggests that the incidence of positive

objective findings would have been higher. Numbness lasted up to six months or longer in a few cases without progression of disease or development of other neurological deficits.

Numbness and Pain in the Thighs.—This group of patients is distinguished from the previous group with numbness in the thighs because of the resemblance of the complaints to the neurological entity known as "meralgia paresthetica," a disease affecting the lateral femoral cutaneous nerve. Of the 19 individuals who noted this type of difficulty, ten were women. Pontocaine hydrochloride with glucose was the anesthetic in 15 cases and Pontocaine hydrochloride with glucose and epinephrine in the other four. A 16 gauge needle was used for the administration of continuous catheter spinal in two cases, and 22 or 24 gauge needles in the remainder. All lumbar punctures were performed below the third intervertebral space. In five instances, more than one insertion of the needle was made with blood-tinged cerebrospinal fluid obtained in one case. Seven persons experienced paresthesias at the time of lumbar puncture, but a possible relation to the subsequent development of neurological disease was present only in two. The sensory anesthetic levels attained were up to the third thoracic dermatome. The operation required the use of stirrups in six cases while, in one other, the numbness appeared related to a femoral herniorrhaphy performed on the same side. Still another patient had had trouble with his legs before operation and one more patient had experienced numbness in the opposite leg before operation. Neither thigh was affected more frequently than the other. Objective sensory loss was present in seven persons and absent in five, but a neurological examination was not performed in the others. Complaints in addition to numbness bore the following descriptions: aching, soreness, tingling, drawing, and annoying.

DISCUSSION

In this report we have described the varieties of sensory neurological symptoms and signs found in 71 of a total of 8,460 patients who had been given spinal anesthesia and who were followed for at least a six-month period after anesthesia. Before discussing the meaning of these findings we must inquire if the complaints are genuine. Many of these people were apparently symptom free when seen in the immediate postoperative period, yet described neurological symptoms as having existed from the time of operation, when they were interviewed or written to six months later. There is little doubt that this type of investigation sensitizes the individual to the possibility of development of disease, and that he may therefore associate minor findings and complaints with the previously given anesthetic. Yet we believe that the complaints are genuine. Similar findings were not encountered in the control series of patients given general anesthetics. Though sensory defects were not always found on examination, a meticulous examination may be required to discover minute areas of sensory loss associated with the destruction of only a few sensory nerve fibers. The important fact is that all of these complaints were of minor significance in the lives of the

individuals affected. The complaints were not of a progressive nature nor were they associated with other neurological defects. There were no instances of the cauda equina syndrome, of transverse myelitis, or of meningitis.

If we can accept the fact that we have discovered definite neurological disease, albeit of minor significance, we must inquire as to the cause. The neurological sequelae of spinal anesthesia may be related either to the trauma of lumbar puncture or to the injection of the anesthetic agent.[2, 3] We will report at another time those complaints which were, in our opinion, related to lumbar puncture or a decrease in cerebrospinal fluid pressure. They are: headache, ocular and auditory abnormalities, and sequelae related to traumatic attempts at lumbar puncture. Numbness usually is not found to be associated with the lumbar puncture sequelae. Few of the 71 individuals whose difficulties are presented here had headaches. There were comparatively few instances of traumatic lumbar puncture, and on only a few occasions was blood-stained cerebrospinal fluid obtained. When paresthesias were produced at the time of lumbar puncture, they bore no obvious relation to the subsequent site of neurological involvement. We must conclude then that the trauma of lumbar puncture played little part in the development of the disease. Was trauma of another type responsible? Can the type of operation performed or the mechanical factors associated with operation be implicated? In a number of instances the complaints may be related to the positioning of legs in stirrups. There might have been a direct relation in instances where varicose veins were ligated, hemorrhoidectomy performed or herniorrhaphy carried out in close proximity to the area of numbness. These cases do not comprise a large share of those reported. A relation to position on the operating table, to the application of restraining straps, or to the subsequent intramuscular injection of antibiotics into the thigh cannot be established.

We are left with a consideration of the part played by the anesthetic injected into the subarachnoid space. One fact emerges from this study, that is, the complaints were confined almost entirely to the lumbar and sacral areas of the body. This is the general area of the spine at which the lumbar puncture is made and consequently where the concentration of anesthetic in contact with neural tissues is greatest. No relation between the anesthetic drugs injected into the subarachnoid space and the number of complications was found. The proportion of individuals given Pontocaine hydrochloride and glucose or Pontocaine hydrochloride and glucose and epinephrine in the 71 patients differs in no way from that of the entire series. The factors of weighting the anesthetic with glucose and the position at the time of injection of the anesthetic could not be related to the side on which difficulty was subsequently experienced.

It seems likely, then, that these neurological complaints are related in a nonspecific way to the injection of the anesthetic agent. Increased numbers of cells in the cerebrospinal fluid following spinal anesthesia suggest that a transient sterile type of myelitis or meningitis may be produced during spinal anesthesia.[4, 5] Neurological sequelae have followed the injection of various foreign

substances into the subarachnoid space.[6] The delicacy of spinal structures and their peculiar vascularity almost invites trouble if there be trespass. The encouraging aspect of the cases reported here is the minimal nature of the resultant disease. We feel certain that this good fortune is due to the careful application of spinal anesthesia, in the choice of the patient for this technique, and in the administration of the anesthetic as described in the first report.[1] A final word about the similarity of the neurological complaints described here and meralgia paresthetica. The latter disease is characterized by the appearance of numbness and paresthesias in the area of distribution of the lateral femoral cutaneous nerve. It is not an uncommon ailment.[7, 8] The cause of the disease is unknown, having been variously attributed to arthritic disease in the lower spine, to spinal trauma, to excessive tobacco smoking, or to certain lower abdominal stresses such as pregnancy, the wearing of a truss, or a cartridge belt. The course of the lateral femoral cutaneous nerve in the retroperitoneal tissues and lower abdomen, its proximity to the anterior superior spine of the ilium, and finally its penetration of the fascia lata suggests that the nerve may be inordinately susceptible to trauma. Is it a coincidence that in approximately one-half of the patients reported in this paper the area involved in numbness coincided with that of the distribution of the lateral femoral cutaneous nerve? It hardly seems possible that specific nerve fibers such as those contributed to the lateral femoral cutaneous nerve can be selectively affected by a chemical substance injected into the subarachnoid space. Which of the various mechanical factors associated with spinal anesthesia and operation play a role in the development of numbness in the thigh after anesthesia cannot be elucidated from the present study.

SUMMARY AND CONCLUSIONS

Seventy-one persons or 0.8 per cent of a total of 8,460 individuals given 10,098 spinal anesthetics had residual signs or symptoms of numbness following anesthesia. In the overwhelming number of patients, the numbness was restricted to the lumbar and sacral areas of the body. None of these cases had other neurological signs, the disease was not progressive, and most of the complaints had disappeared after a period of six months. There were no cases of the cauda equina syndrome, of myelitis, or of meningitis. An analysis of the factors associated with administration of the spinal anesthetic and the operation performed suggests that the spinal anesthetic injected rather than the lumbar puncture played a nonspecific part in the development of the numbness. In contradiction to this conclusion is the fact that at least one-half of the cases reported have a close similarity to the neurological disease entity "meralgia paresthetica." The factors in spinal anesthesia which lead to a disturbance in the lateral femoral cutaneous nerve have not been elucidated. The complaints reported here were of minor significance in the lives of the individuals affected. The fact that such complications have occurred at all stresses all the more the necessity for the careful application of spinal anesthesia.

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ANESTHESIA IN THE SPLANCHNICECTOMIZED PATIENT

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INTRODUCTION

OPERATIONS involving the interruption of the splanchnic nerves or removal of these nerves with portions of the dorsal and lumbar sympathetic chains have been performed for the past twenty-five years. Smithwick[1] in 1951 reported about 2,000 patients treated surgically for essential hypertension and has now performed approximately 2,500 bilateral splanchnicectomies. Considering that this represents the experience in only one clinic, and that similar operations are performed in many centers throughout this country and abroad, it is apparent that the number of splanchnicectomized patients is formidable. Many of these patients will necessarily appear at various clinics throughout the country for other types of surgery. The problem of how their cardiovascular systems react to the stress of further surgery and anesthesia has prompted us to study the patients at the Massachusetts Memorial Hospitals who have received anesthesia for surgery following splanchnicectomy during the period from 1947 to the present time.

RESULTS

From March, 1947, to July, 1954, there were 138 operations on 89 previously splanchnicectomized patients. The youngest was 22 years old and the oldest 62, 44 being between the ages of 40 and 50. There were 50 women and 39 men. Except for 2 who had angina, 1 whose chief complaint was abdominal pain, and 1 with a diagnosis of nephralgia, the indication for splanchnicectomy was essential hypertension. The interval between splanchnicectomy and secondary operation is shown in Table I, and procedures in Table II.

There were 18 operations between stages of splanchnicectomy, 2 performed within one week of the first stage, 6 within two weeks, 4 within one month, and 6 within sixty days. Table III shows the procedures performed between stages.

Inhalation-endotracheal anesthesia was used in 85 cases, spinal anesthesia in 18, and intravenous and inhalation were combined in 23. In the remaining patients, local anesthesia alone, or in combination with intravenous barbiturates, was elected. Barbiturate induction employing sodium pentobarbital, sodium thiopental, or sodium hexabarbital was used in 44 patients. A neuromuscular blocking agent was used in 23 patients, Mytolon chloride being most frequently selected.[2]

Twenty-three operations lasted one-half hours or less, and a total of 117 operations lasted two and one-half hours or less. The longest operation was eight hours.

Received for publication March 7, 1955.

TABLE I. TIME INTERVAL BETWEEN SPLANCHNICECTOMY AND SECOND OPERATION

Less than 1 year	53
1 year	14
2 years	16
3 years	15
4 years	13
5 years	12
6 years	5
7 years	3
8 years	5
10 years	2

In management of these patients, we were concerned that blood pressure be maintained at adequate levels. Vasopressors were not required in 86 patients either during surgery or in the immediate postoperative period. Twenty-two patients received phenylephrine hydrochloride solution 1 to 100,000 intravenously by continuous drip, both during and following surgery. Twenty-eight patients received varying amounts of this vasopressor during anesthesia only, and 2 patients received it only during the postoperative period. Of the total number of patients receiving phenylephrine hydrochloride postoperatively, 7 received

TABLE II. SURGICAL PROCEDURES

Intra-abdominal	
Gastric	7
Gall bladder	13
Small bowel	4
Genitourinary	
Renal and adrenal	10
Ureter, bladder, urethra	12
Pelvic	
Perineal	7
Intrapelvic	5
Sympathectomy	
Dorsal	5
Transthoracic	11
Lumbodorsal	2
Lumbar	1
Revision Splanchnicectomy Wound	
Soft tissue	14
Rib resection	6
Root section	5
Neurofibroma	1
Thoracic duct sinus	1
Thyroid	3
Dental	3
Soft tissue	12
Herniorrhaphy	7
Ear, nose, throat	3
Rectal	4
Thoracotomy	2

TABLE III. SURGICAL PROCEDURES BETWEEN STAGES OF SPLANCHNICECTOMY

Intraspinal root section	2
Cholecystectomy	6
Wound revision	6
Rib resection	1
Breast biopsy	1
Dilatation and curettage	1
Excision neurofibroma	1

fractional doses. The largest number of patients needed administration of any vasoconstrictor for one hour or less. The longest time recorded was eighteen hours.

TABLE IV. POSTOPERATIVE COMPLICATIONS

Pulmonary	
Pneumonia	1
Atelectasis	3
Postoperative pneumothorax	1
Pulmonary edema	1
Pleural effusion	3
Circulatory	
Shock	2
Profound blood pressure drop	2
Neurological	
Cerebrovascular accident	1
Headache	2
Others	
Low-grade temperature	1
Nitrogen retention	1
Phlebitis of arm	1

There were 19 postoperative complications, as shown in Table IV. In this total series there were 3 deaths. The cause of death in 1 patient was recorded as being due to his surgical disease. One patient expired from electrolyte imbalance. The third patient, moribund on arrival in the operating room, expired during induction of anesthesia. This was a 40-year-old patient who had a bilateral lumbodorsal splanchnicectomy and developed a massive mesenteric thrombosis eighteen days later, resulting in resection of 20 feet of small intestine. Eighteen days following the resection, an exploratory laparotomy and left phrenic nerve crush were performed for uncontrollable hiccoughs. Seventeen days later the patient became unconscious and a diagnosis of diffuse encephalitis secondary to cerebral anoxia or emboli was made. Eleven days following the appearance of unconsciousness, gastrostomy was attempted. Cyclopropane and oxygen were administered, and when the skin incision was made, pulse and blood pressure became unobtainable. Despite resuscitative measures, including cardiac massage, the patient did not respond.

COMMENT

Even though splanchnicectomized patients are in the young or middle-aged group, and appear in satisfactory general condition, they may exhibit considerable circulatory instability. This is likely to be more marked if the surgical disease or any other factor has caused deterioration in the general physical status. When anesthesia is induced, some of these patients show an initial drop in blood pressure such as is often observed during anesthesia for second stage splanchnicectomy. Untreated, this may result in cardiovascular collapse with serious cardiac and cerebral sequelae, or may even be fatal. Often, simply lightening anesthesia results in prompt recovery. If this is not the case, transfusion with whole blood and administration of a vasoconstrictor agent should be started immediately. For this reason, in many cases we habitually had

ready an infusion of phenylephrine hydrochloride connected to the intravenous equipment. This could be started within a few seconds after the blood pressure drop was observed.

Selection of the anesthetic agent or method is less important than an understanding of the physiologic principles underlying the management of the patients we are discussing. These basic principles are support of circulation, adequate blood replacement, and satisfactory oxygenation.

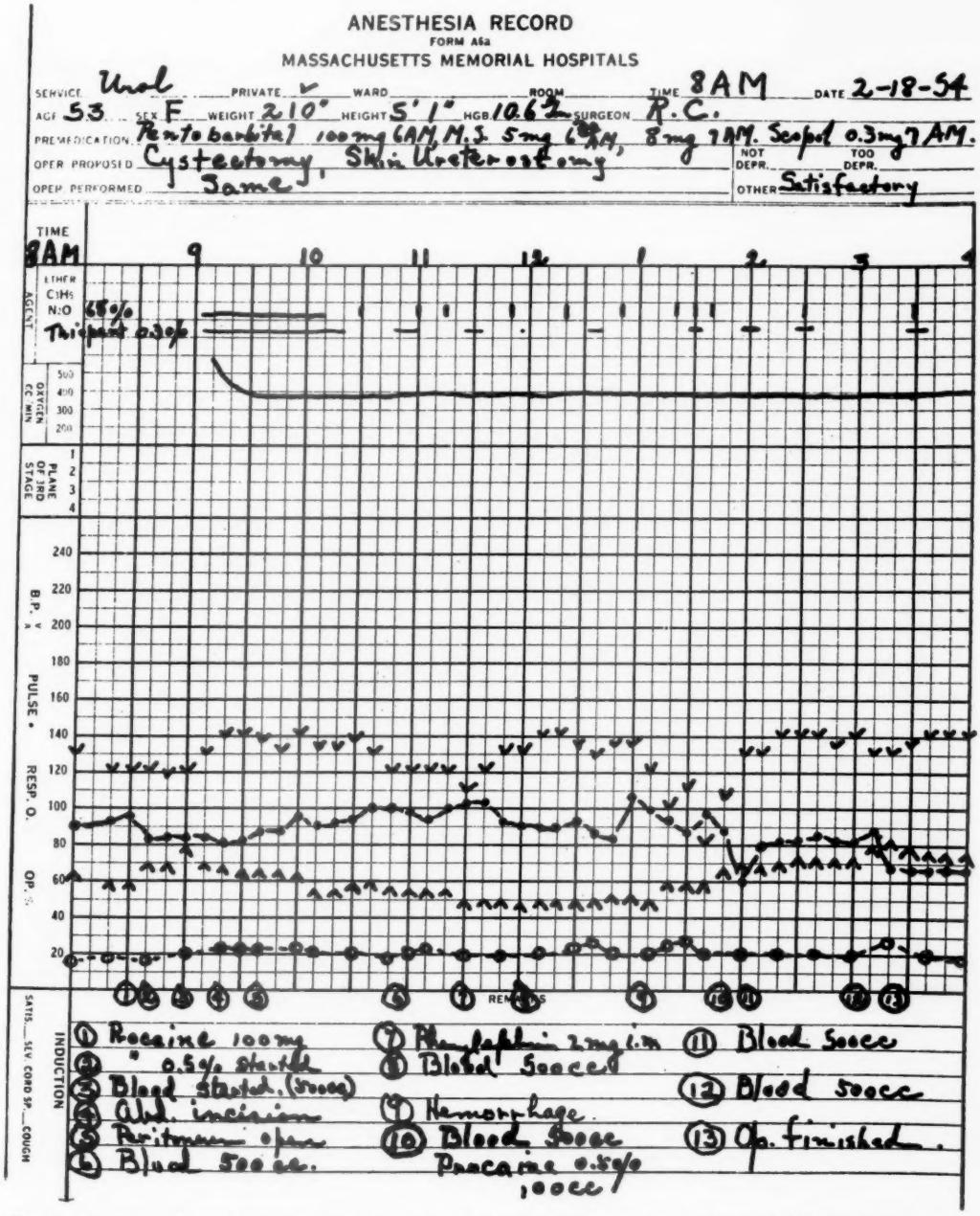
ANESTHESIA RECORD
FORM A6a
MASSACHUSETTS MEMORIAL HOSPITALS
SERVICE Urol PRIVATE ✓ WARD ROOM TIME 8AM DATE 2-18-54
AGE 53 SEX F WEIGHT 210# HEIGHT 5'1" HGB. 10.6 SURGEON R.C.
PREMEDICATION Pentobarbital 100 mg 6AM, M.S. 5mg 6AM, 8mg 7AM. Scopol 0.3mg 7AM.
OPER. PROPOSED Cystectomy, Skin Ureterostomy
OPER. PERFORMED Same
NOT DEPR. TOO DEPR. OTHER Satisfactory
TIME 8AM 9 10 11 12 1 2 3 4
AGENT ETHER C3H8 N2O 65% Trilene 0.3%
OXYGEN 2L MIN 500 400 300 200
PLANE OF 3RD STAGE 1 2 3 4
B.P. PULSE RESP. O. OP.
240 220 200 180 160 140 120 100 80 60 40 20
REMARKS
INDUCTION SATIS.—SLV CORD SP.—COUGH
① Procaine 100 mg
② " 0.5% Started
③ Blood started. (500cc)
④ Abd. incision
⑤ Peritoneum open
⑥ Blood 500 cc.
⑦ Phenylephrine 2mg i.m.
⑧ Blood 500cc
⑨ Hemorrhage
⑩ Blood 500cc
Procaine 0.5% 100cc
⑪ Blood 500cc
⑫ Blood 500cc
⑬ Op. finished.

Fig. 1.—Record of continuous spinal anesthesia for cystectomy and bilateral skin ureterostomy.

It was previously noted that general anesthesia was the method usually chosen, and ether the agent most frequently used. Early in our experience, when we hesitatetd to employ curare or other neuromuscular blocking agents with these patients, we were concerned with the profound falls in blood pressure which occurred when ether anesthesia was deepened for intubation or to produce relaxation sufficient for deep abdominal work. This type of episode should be considered ominous in view of Brewster's demonstration of the myocardial depression caused by ether, especially in sympathectomized subjects.[3] We have found that, with care, neuromuscular blocking agents can be used safely and are invaluable in avoiding deep levels of anesthesia for intubation and in situations where abdominal relaxation is imperative. From what we had learned about handling them during splanchnicectomies, we felt that in our hands ether was a safer agent. Since this series extends back to 1947, recently light inhalation technique employing cyclopropane-oxygen has supplanted ether-oxygen as the major anesthetic agent.

Spinal anesthesia properly employed is safe and in many cases may be the method of choice. Fig. 1 shows a record of continuous spinal anesthesia in a patient splanchnicectomized seven years previously who had returned for a cystectomy and bilateral ureteral transplant. Anesthesia lasted eight hours, and aside from one hypotensive episode following hemorrhage, the anesthesia course was uneventful. Splanchnicectomized patients have had the sympathetic ganglia from the eighth dorsal through the first or second lumbar levels removed with consequent paralysis of vasoconstrictor fibers at these levels. For this reason, spinal anesthesia below the level of the eighth dorsal segment is likely to have little or no effect upon blood pressure. However, if a hypotensive episode does occur, administration of phenylephrine hydrochloride or other vasoconstrictor agent ensures prompt control of the situation.

It is interesting to note the frequency of cholecystectomy between stages of splanchnicectomy. Anesthesia in these cases offered no problems, and these patients appeared quite stable.

When the use of a vasoconstrictor agent is indicated, we prefer phenylephrine hydrochloride administered by continuous infusion because it allows free choice of the anesthetic agent. The drip method of administration produces a sustained elevation of blood pressure and the occurrence of tachyphylaxis is rare. If a satisfactory blood pressure response is not obtained by phenylephrine we were of the opinion that blood replacement is inadequate and additional transfusion is indicated. When replacement is certainly adequate and hypotension persists, good results are sometimes obtained by using some other vasoconstrictor amine such as l-norepinephrine. It is evident that the majority of patients in this series did not require vasoconstrictors.

SUMMARY

1. It is likely that an increasing number of previously splanchnicectomized patients needing further surgery will appear at scattered clinics through the country.

2. A review of 138 anesthetic procedures in 89 patients previously splanchnicectomized is presented.

3. All types of surgery following bilateral splanchnicectomy at various times are included.

4. Splanchnicectomized patients are able to withstand the stress of anesthesia and surgery provided basic principles of support of circulation, blood replacement, and adequatae oxygenation are scrupulously observed.

5. Deep levels of general anesthesia should be avoided, neuromuscular blocking agents being judiciously used in preference.

6. When these requirements are met, the need for vasoconstrictor agents is infrequent.

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BRANCHED ARTERIAL HOMOGRAFTS

An Experimental Study

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AT THE present time there is widespread use of the replacement of the abdominal aorta and its major branches with branched arterial homografts in man. In contrast to this current clinical practice, there has been surprisingly little attempt to determine the fate of these branched arterial homografts in the experimental laboratory. Aside from Dalem's[1] publication, all of the reported studies have concerned the replacement of straight arterial segments. It appeared pertinent at this time to report our experience with these branched homografts in the experimental animal.

PROCEDURE

The abdominal aorta in dogs divides into three branches (Fig. 1). Aside from the two external iliac vessels, there is a median branch which is the continuation of the abdominal aorta. This median branch is very short (0.5 to 1.0 cm. long) and divides into the two hypogastric arteries and continues as the mid-sacral artery. Thus, it is evident that replacement of this segment requires four anastomoses rather than the three that are necessary in human beings.

From donor dogs, within four hours of death, we resected the abdominal aorta just distal to the renal arteries and approximately 6 to 8 cm. of each iliac artery as well as 1 cm. of the middle branch.

Three methods of preserving the homografts were employed. (1) The technique described by Gross and associates,[2] using a modified Tyrode's solution, penicillin, streptomycin, and homologous dog serum was used in the first group of dogs. These grafts were stored at 4° C. for varying periods of time, but not over 21 days. (2) Homografts were frozen quickly in a bath of dry ice and alcohol and stored at –70° C. from 7 to 99 days.[3] (3) Homografts were prepared by freeze-drying and then preserved in a vacuum from 45 to 199 days as described by Pate and Sawyer.[4]†

These preserved grafts were placed in dogs. Under Nembutal sodium anesthesia, given either intravenously or intraperitoneally, the abdomen was entered through a low midline incision. The posterior parietal peritoneum was opened and exposure of the aorta and iliac arteries was easily accomplished. Non-crushing arterial clamps were applied to the aorta just below the renal arteries

Received for publication Jan. 13, 1955.

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†These lyophilized graphs were prepared at the Naval Medical Center at Bethesda, Md., according to the technique they are currently employing.

and the iliac arteries, about 10 cm. from the aortic trifurcation. Application of the clamp on the middle branch was at times difficult due to its extremely short length but was successfully accomplished in each case. The vascular segment between the clamps was then removed and the graft sutured in place. A continuous Carrel suture of No. 5-0 silk was used. After completion of the four

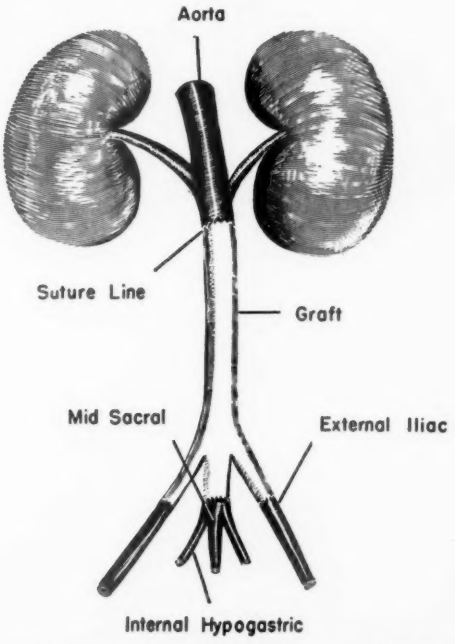

Fig. 1.—Diagram showing the aorta in a dog with graft in place.

Fig. 2.—Photograph at the operation showing all four anastomoses with no leakage.

anastomoses, the distal clamps were removed. In a few cases, one or two sutures were required to stop anastomotic leaks, and then the proximal aortic clamp was removed. Neither plastic shunts to maintain circulation nor anticoagulants were used. The usual length of time consumed in making the anastomoses was

forty-five to fifty minutes. The longest time the aorta was completely occluded was seventy minutes. The patency of the graft was noted before closure by palpation of the three branches distal to the anastomoses. In general, the grafts were the approximate size of the host aorta. The abdomen was closed without drainage.

RESULTS

Grafts Preserved in Solution (Table I).—Twelve dogs were operated upon and two died. One dog never recovered from anesthesia and died within twenty-four hours with an intact graft. This animal was eliminated from the study. The other dog, counted in our study, died on the fifth postoperative day of unknown causes, with an excellent functioning graft.

TABLE I

NO.	WEIGHT IN POUNDS	GRAFT PRESERVED (DAYS)	DURATION—POSTOPERATIVE DAYS	REMARKS
1	35	20	86	Clinically well, sacrificed; no thrombosis, excellent graft
2	32	5	5	Expired; no thrombosis; excellent graft; cause of death obscure
3	30	19	536	Clinically well; sacrificed; thrombosis of both external iliac portions of graft by aortogram on 111 days as well as at autopsy
4	25	2	536	Clinically well; sacrificed; excellent graft
5	25	7	524	Clinically well; sacrificed; thrombosis of right external iliac portion of graft by aortogram at 98 days as well as at autopsy
6	35	20	526	Clinically well; sacrificed; thrombosis of both external iliac portions of graft by aortogram at 104 days and autopsy
7	25	21	38	Paraplegia; sacrificed; complete thrombosis of aorta-aorta anastomosis; remainder of graft patent
8	30	5	510	Clinically well; sacrificed; thrombosis of left external iliac portion of graft by aortogram at 78 days and at autopsy; a small thrombus in aortic segment of graft
9	40	6	505	Clinically well; sacrificed; delivered litter of six 53 days postoperatively; excellent functioning graft; one small placque at aorta-aorta anastomosis
10	30	7	1	Expired; excellent graft; cause of death obscure
11	35	1 hour	470	Clinically well; sacrificed; excellent graft
12	35	7	470	Clinically well; sacrificed; excellent functioning graft; one small thrombus in aortic portion of graft

Ten dogs were studied from 38 to 536 days. Only one dog exhibited clinical signs of thrombosis. Paralysis of the right hind leg was noted in twenty-four hours and progressed to paraplegia in forty-eight hours with absent femoral pulsations. The general condition was excellent at time of sacrifice on the thirty-eighth postoperative day. Autopsy demonstrated a complete thrombosis at the aorta-aorta anastomosis arising 1 cm. proximal to the anastomosis in the

host aorta. The other three anastomoses were patent. Perhaps the host aorta was unduly traumatized with the arterial clamp because it was at this site that the thrombosis was found.

Nine dogs remained active and well. One dog delivered a normal litter on her fifty-third postoperative day. These dogs were followed from 86 to 536 days, with seven of these dogs studied over one year.

Thrombosis of both external iliac portions of the graft was seen in two dogs, (Fig. 3) while thrombosis of a single external iliac portion of the graft was noted in two other dogs.

Fig. 3.—Graft preserved 20 days in solution. 526 days postgrafting demonstrated thrombosis of both external iliac portions of graft. (Table I, No. 6.)

The remaining five dogs had satisfactory functioning patent grafts. Two of these dogs had small areas of thrombosis in the aortic portion of the graft, but with a satisfactory lumen. Three dogs had excellent functioning grafts without evidence of thrombosis or calcification. Aneurysmal dilatation was absent from all grafts.

Frozen Grafts (Table II).—Fourteen aortic trifurcation frozen preserved grafts were implanted into donor dogs. One dog did not recover from the anesthesia, and the exact cause of death was obscure. The remaining thirteen dogs were studied from 5 to 205 days after surgery.

Five grafts were completely thrombosed. Three of these dogs had early hindleg paralysis, and subsequent gangrene of the legs was noted in the early

postoperative course. One dog appeared to be well but suddenly expired on the forty-second postoperative day of a pulmonary embolism and was found to have complete thrombosis of the graft. Another dog was well but on sacrifice, 199 days postsurgery, the graft was almost completely occluded by a thrombus with a relative stenosis of the aorta-aorta anastomosis (Fig. 4).

TABLE II. FROZEN GRAFTS

NO.	WEIGHT IN POUNDS	GRAFT PRESERVED (DAYS)	DURATION—POSTOPERATIVE DAYS	REMARKS
1	38	7	6	Expired; complete thrombosis of graft; gangrene of legs
2	27.5	54	16	Sacrificed; complete thrombosis of graft; gangrene of legs
3	44	28	42	Clinically well; died of pulmonary embolus left lower lobe; complete thrombosis of graft
4	34	21	199	Clinically well; complete thrombosis of graft
5	45	35	205	Well; sacrificed; excellent functioning graft; no calcification; one small thrombus aortic portion of graft
6	38	44	203	Well; sacrificed; no thrombosis; calcification of aortic portion of graft
7	45	42	0	Died on table; anesthesia problem
8	45	96	185	Clinically well; marked narrowing of aortic anastomosis; graft was atrophied rough yellow lining
9	33	66	5	Died; thrombosis entire graft; gangrene of legs
10	26.5	14	178	Sacrificed; no thrombosis or calcification; excellent graft
11	20	16	176	Clinically well; sacrificed; thrombosis on pedicle at site of ligation of branches on graft; superficial ulcerations of the remaining portions of graft; right iliac orifice narrowed by middle sacral anastomosis; open no thrombosis but atrophied
12	22.5	21	106	Clinically well; sacrificed; no thrombosis or calcification; excellent graft
13	26	61	71	Clinically well; calcification of aortic graft; thrombosis in the right iliac only; completely occluded
14	25	99	64	Clinically well; calcification of entire graft; complete thrombosis of right iliac; small thrombosis of aortic portion of graft

One dog was apparently well but at sacrifice, 185 days postsurgery, was found to have a very narrow aortic anastomosis with a patent but atrophied graft (Fig. 5).

One dog was apparently well for 176 days but at sacrifice was found to have an atrophy of the right external iliac portion of the graft due to narrowing of the iliac orifice by the adjacent middle sacral anastomosis. There were superficial ulcerations and one thrombosis in the aortic portion of the graft.

Two grafts were completely calcified and the right iliac portion of each was completely thrombosed (Fig. 6). Both of these dogs were doing well for over two months postsurgery. One graft was functioning well and without thrombosis for 203 days, but the aortic portion of the graft was heavily calcified.

Fig. 4.—Frozen graft preserved 21 days. Clinically well. Sacrificed 199 days postsurgery. Apparently well. Partial stenosis of aorta-aorta anastomosis with a thrombus filling the graft. (Table II, No. 4.)

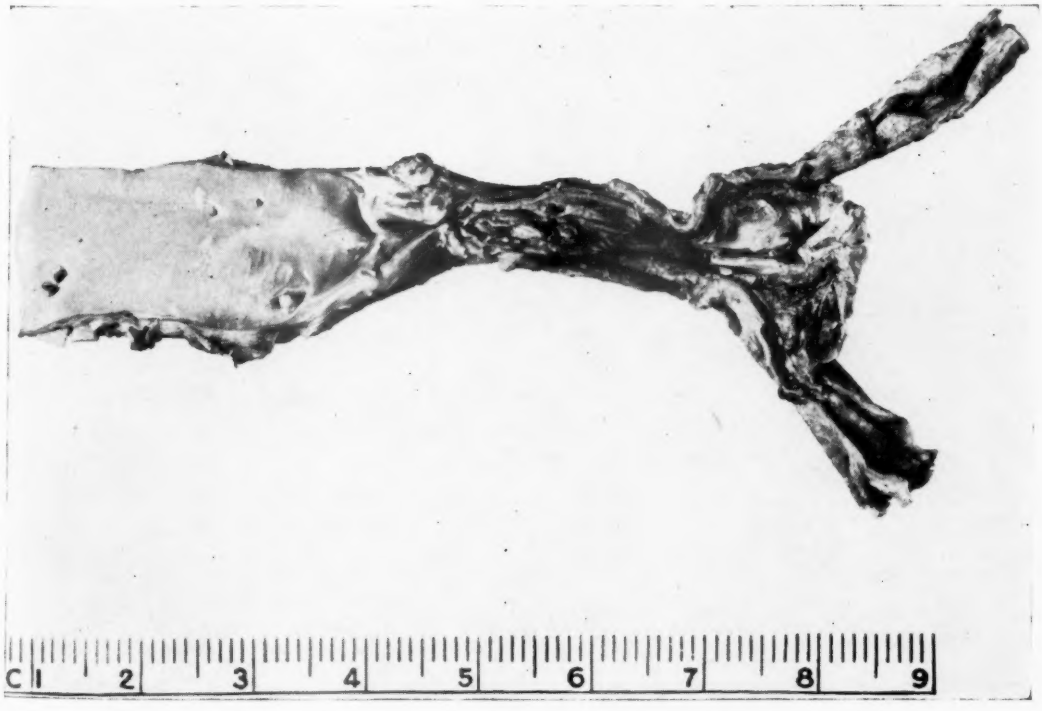

Fig. 5.—Frozen graft preserved 96 days. Sacrificed 185 days postsurgery. Apparently well. A very narrow anastomosis with a patent but atrophied graft. (Table II, No. 8.)

Fig. 6.—Frozen graft preserved 61 days. Sacrificed 71 days postsurgery. Apparently well. Calcification of entire graft with thrombosis of the right external iliac artery. (Table II, No. 13.)

Fig. 7.—Frozen graft preserved 14 days. Sacrificed 178 days postsurgery. Apparently well. Excellent functioning graft. (Table II, No. 10.)

Three grafts were functioning well with no evidence of calcification for over three months. One of these grafts had one small area of thrombosis in the aortic portion of the graft 205 days postsurgery; the other two grafts were perfect (Fig. 7).

Lyophilized Grafts (Table III).—Ten dogs were operated upon. One dog eviscerated on the sixth postoperative day with a patent graft that had a small thrombus at the right iliac anastomosis which was not occluding the lumen.

The second dog died on the fourth postoperative day from a thrombosis at the aortic anastomosis associated with a leak and hemorrhage from the aortic suture line.

TABLE III

NO.	WEIGHT IN POUNDS	GRAFT PRESERVED (DAYS)	DURATION—POSTOPERATIVE DAYS	REMARKS
1	40	199	6	Expired; evisceration; patent graft; small thrombus at right iliac anastomosis; not obstructive
2	30	101	75	Sacrificed; hindquarter paralysis immediately with complete recovery; complete thrombosis of both iliacs; middle sacral open; one small thrombus on aortic portion of graft
3	39	106	70	Clinically well; complete thrombosis of entire graft
4	40	45	131	Clinically well; sacrificed; complete thrombosis of right iliac; one small thrombus in aortic portion (nonobstructive)
5	35	148	30	Clinically well; sacrificed; almost complete obstruction at aortic anastomsis with patent but atrophic graft
6	35	141	42	Clinically well; sacrificed; perfect graft
7	40	115	78	Clinically well; sacrificed; thrombosis entire graft; aortic anatomosis not narrowed
8	25	136	44	Clinically well; sacrificed; patent graft; small thrombus aortic portion at site of ligation of branches
9	38	109	49	Clinically well; sacrificed; narrowing at aortic anastomosis; entire graft thrombosed
10	25	150	4	Expired; thrombosis at aortic anastomosis with rupture at aortic anastomosis with hemorrhage

The remaining eight dogs were sacrificed after periods up to 131 days. One dog developed transient hindquarter paralysis, which at autopsy demonstrated complete thrombosis of both iliac portions of the graft as well as a small nonoccluding thrombus of the aortic segment. Seven dogs were clinically well. However, three of these dogs had complete thrombosis of the entire graft. In another animal there was almost complete stenosis at the aortic anastomosis with a patent but atrophied graft. There was one complete thrombosis of the right iliac portion of one graft associated with a small nonobstructive aortic thrombosis. Another graft was patent but had a small nonoccluding thrombus in the aortic portion. There was one perfect graft throughout. There was no calcification or aneurysm formation in these lyophilized graphs.

Comparative results are summarized in Table IV.

TABLE IV. COMPARATIVE RESULTS

	TYRODE'S	FROZEN	LYOPHILIZED
Total number	11	13	10
Perfect grafts	5	2	1
Satisfactory—nonoccluding thrombus	2	2	2
Complete thrombosis	1	5	3
Thrombosis—both iliac segments	2	0	1
Thrombosis—single iliac segment	2	2	1
Calcification	0	3	0
Rupture	0	0	1
Stenotic aortic anastomosis—patent graft	0	1	1

DISCUSSION

In view of the growing popularity of arterial grafts, both of the homograft type and the type using synthetic materials, the long-term fate of which no one yet has any knowledge, it appeared to us that branched grafts offered a more severe test than the straight grafts usually used experimentally. We started these experiments before the first human replacement of a branched aortic segment had been carried out. After surveying all the preserving and grafting techniques presented since that time, we are even more firmly convinced that these branched grafts offer a better test of methods of preservation.

A survey of the failures in all our dogs shows that if any anastomosis was open, it was always the common trunk of the internal iliac artery. In the twenty-two dogs in which the aortic segment of the graft showed a completely satisfactory lumen, the common trunk of the internal iliac artery (the straight segment) was always patent, whereas thrombosis occurred in eleven of the forty-four branching segments. This would seem to indicate that the eddy currents, and so on, in the branching segments, facilitated thrombosis. In how many instances thrombosis started in one or more of these branches and subsequently extended to complete thrombosis of the entire system is difficult to state.

From this small series of experiments, sweeping conclusions are unjustified. However, some facts seem inescapable. The grafts preserved in Tyrode's solution even after over 500 days of replacement in the dogs looked in the gross state amazingly like the host aorta, with no shortening, wrinkling, or calcification. Thrombosis occurred in some instances as detailed, but the remainder of the vessel wall looked practically normal.

In the vessels which had been prepared and preserved in the frozen state, calcification was noted as early as sixty-four days after implantation. Shrinkage of the grafts occurred only in the grafts that were preserved by freezing or lyophilization.

It is worthy of note that rupture of the anastomosis occurred in only one animal, and this was associated with thrombosis.

The branched vessels used in this study were in most instances less than 6 mm. in diameter (external iliac artery). There are obviously few vessels of this diameter which would be subject to grafting in the human being.

SUMMARY

1. The fate of branched arterial homografts to replace the terminal aorta and its three major branches was determined in 35 dogs. Three methods of preserving the aortic homografts were used: (1) modified Tyrode's solution; (2) quick freezing in dry ice and alcohol and preservation at –70° C.; and (3) lyophilization and preservation under a vacuum according to the technique of Pate and Sawyer.[4]

2. The relative efficacy of the grafts using the three techniques has been presented. Satisfactory grafts were obtained in 7 of 11 in the "Tyrode" grafts, 4 out of 13 in the frozen grafts, and 3 out of 10 in the lyophilized grafts. The straight segments of the grafts were patent in 10 out of 11 of the "Tyrode" grafts, in 8 of the 13 frozen grafts, and in 6 of the 10 lyophilized grafts. Calcification occurred in 3 of the frozen grafts. Atrophy to a marked degree occurred in 3 of the frozen grafts and in one of the lyophilized grafts.

3. Possible reasons for the unfavorable results in branched grafts as opposed to straight grafts previously reported have been presented.

4. The use of branched grafts is urged experimentally to test other types of vessel replacement.

CONCLUSIONS

1. On the basis of this study, preservation of homografts in modified Tyrode's solution was superior to preservation in the frozen state or after lyophilization, when using branched arterial grafts to replace the terminal aorta and its three major branches in the dog.

2. Lyophilized grafts appeared to be superior to continuously frozen grafts in that calcification did not occur.

Grateful acknowledgment is extended to Drs. Francis Chanatry, Herman Rustad, and Russell Greenhalgh for their interest and assistance in this undertaking.

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ADAPTATION OF HOMOLOGOUS AORTIC GRAFTS FOR SURGICAL CORRECTION OF INFANTILE COARCTATION OF THE AORTA

A Preliminary Report

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USE of homologous aortic grafts in the treatment of adult coarctation of the aorta is a well-established procedure.[1, 2] In most adult coarctations, the narrow segment of obliteration is readily amenable to local excision and end-to-end anastomosis of the stumps of the descending aorta. In a few cases, however, the gap resulting from excision of a moderately extensive segment of adult coarctation is too long to permit end-to-end anastomosis, and aortic homologous grafts have been utilized to bridge the gap. The results have been eminently satisfactory. Recent work with plastic substitutes for aortic grafts encourages the hope that artificial aortic prostheses may be similarly used in the future.[3-5]

Infantile coarctation, on the other hand, often cannot be corrected by present surgical procedures. It consists of a relatively long segment of partial obliteration involving the distal aortic arch. It may involve one or both of the carotid vessels and frequently involves the left subclavian artery, causing the characteristic manifestation of hypertension limited to the right upper extremity. Sometimes, it is associated with intracardiac septal defects which act as decompressing mechanisms to shunt blood from the left heart to the right heart. Occasionally, a large patent ductus arteriosus supplies blood to the descending aorta. Local excision of these long segments of infantile coarctation is usually impossible. In most cases, the condition is not compatible with long life.

Post-mortem examinations of patients with infantile coarctation revealed that, in many cases, the coarctation did not extend completely to the base of the heart. A dilated segment of aorta frequently was found from the level of the aortic valve to the point of coarctation at the innominate artery or the left common carotid artery. This suggested that aortic grafts might be used to connect the ascending aortic arch with the descending thoracic aorta, in order to shunt the aortic stream around the infantile coarctation. Successful attempts to replace segments of the aortic arch with homologous grafts have been reported.[6, 7] It was hoped that this principle could be adapted to the precarious surgical risk presented by patients with infantile coarctation by inserting the grafts without attempting to excise the coarctation (Fig. 1).

From the Otho S. A. Sprague Memorial Laboratory and supported by funds from the Chicago Heart Association.

Received for publication April 9, 1955.

PATHOLOGIC VARIATIONS OF COARCTATION OF THE AORTA

The availability of a dilated ascending aortic arch in patients with infantile coarctation was estimated by a review of all operative and autopsied cases entering the Children's Memorial Hospital of Chicago since 1940. One hundred and five cases were collected, and the following types of coarctation of the aorta were noted (Fig. 2).

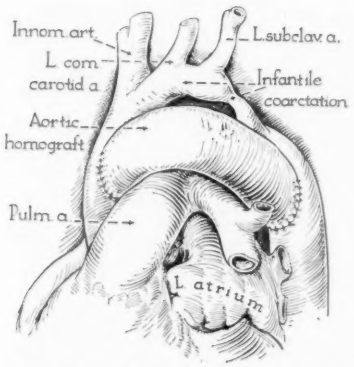


Fig. 1.—Diagram of the operation devised for long infantile coarctation involving the distal two-thirds of the aortic arch. A homologous aortic graft is utilized to shunt the aortic stream from the large ascending aorta to the descending thoracic aorta distal to the coarctation.

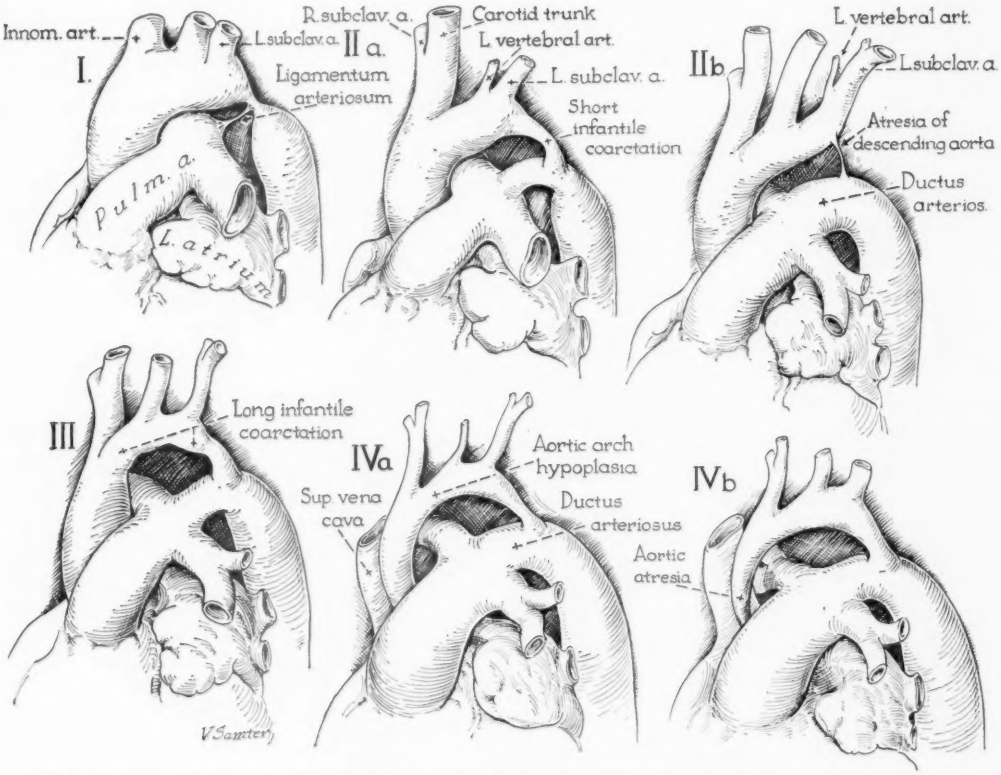


Fig. 2.—Types of coarctation of the aorta encountered in the study of 105 autopsy and operative cases. Type I, adult coarctation of the aorta. Types II-A, II-B, III, IV-A, and IV-B, variants of infantile coarctation of the aorta (see text). I, II a, and II b illustrate variations in the origin of the cephalobrachial arteries associated with coarctation of the aorta.

Type I. Adult Coarctation of the Aorta.—Most of the cases collected were in the familiar operable group of coarctation of the aorta. Fifty-nine patients (56.1 per cent of the collected series) had a narrow segment of coarctation located near the junction of the patent ductus arteriosus with the aorta (Table I). They

TABLE I. DISTRIBUTION OF PATHOLOGIC VARIATIONS OF COARCTATION OF THE AORTA

GROUP	DIAGNOSIS	NUMBER	PER CENT
Type I	Adult coarctation of the aorta	59	56.1
Type II-A	Short infantile coarctation of descending aortic arch	11	10.5
Type II-B	Atresia of descending aortic arch	2	1.9
Type III	Long infantile coarctation of aortic arch	26	24.8
Type IV-A	Hypoplasia of entire aortic arch	3	2.9
Type IV-B	Hypoplasia of aortic arch with aortic valve atresia	4	3.8
	Total	105	100.0

were readily amenable to surgical excision and constituted the major portion of the operative cases included in this collection. No homologous aortic grafts had to be used in these patients. After excision of the coarctation, continuity of the aorta was restored by end-to-end anastomosis of the aortic stumps.

Type II-A. Short Infantile Coarctation of the Aorta.—Eleven patients (10.5 per cent of the collected series) had coarctation of the aorta involving the descending aortic arch from the level of the left subclavian artery to the point of entry of the patent ductus arteriosus into the descending thoracic aorta. In some of these, the ostium of the left subclavian artery was narrowed. In others, it was widely patent. Five patients had a large patent ductus arteriosus entering the descending thoracic aorta, and it was felt that collateral circulation around the coarctation was poorly developed. All but one patient had either interatrial or interventricular septal defects or both. None had associated cardiac anomalies incompatible with surgery.

Since most of these patients entered the hospital prior to the development of surgical correction of adult coarctations, only one of them was operated upon. However, it was felt that the constricted aortic segment in each of them could have been excised and replaced by an aortic graft in the standard manner or that the left subclavian artery could have been utilized to bridge the gap without grafting.[8, 9]

Type II-B. Atresia of the Descending Portion of the Aortic Arch.—There is a variant of the short type of fetal coarctation in which complete atresia of the descending portion of the aortic arch is present. The patent ductus arteriosus is extremely large and empties into the descending thoracic aorta in such a way that it may be mistaken for the aortic arch during operation. The differentiation from truncus arteriosus is made, however, by observation that the cephalobrachial arteries originate from a separate large vessel which emanates from the left ventricle and represents the ascending aorta.

Only two such patients (1.9 per cent of the collected series) were found. They were among the autopsied cases. Both had interatrial and interventricular septal defects, but neither had cardiac anomalies incompatible with surgery.

Had they been encountered at operation, they could have been corrected by inserting a homologous aortic graft between the base of the left subclavian artery and the upper end of the descending thoracic aorta. The large patent ductus arteriosus then could have been divided without any danger of ischemia to the spinal cord.

Type III. Long Infantile Coarctation of the Aortic Arch.—In twenty-six cases (24.8 per cent of the collected series), a long segment of coarctation extended over the distal two-thirds of the aortic arch. The coarctation began just distal to the origin of the innominate artery and involved the ostia of both the left common carotid and the left subclavian arteries. In most cases, a large patent ductus arteriosus communicated with the descending thoracic aorta.

These cases were all derived from autopsy specimens of patients who had died when no operative relief was available. However, only three had other congenital anomalies incompatible with surgery. The remaining 23 (21.9 per cent of the collected series) had no detectable contraindications to operation. Three had small interatrial septal defects, and four had interventricular septal defects. However, all the hearts were well formed and would probably have responded well to the proposed use of an aortic graft to by-pass the coarctation in the distal two-thirds of the aortic arch.

Type IV. Severe Hypoplasia of the Entire Aortic Arch.—Seven autopsy specimens (6.7 per cent of the collected series) had severe hypoplasia of the entire aortic arch. The patients had not survived beyond a few days to a few weeks after birth. Three specimens (Type IV-A) had a small ascending aorta which was open at its base. However, there was severe aortic valvular stenosis and marked hypoplasia of the left atrium and left ventricle. Little could have been accomplished by the insertion of an aortic graft. The remaining four specimens (Type IV-B) represented the final stages of aortic hypoplasia. They had complete atresia of the base of the ascending aorta and the resdiual hypoplastic aortic arch was filled entirely by reflux of cyanotic blood from a large patent ductus arteriosus.

In summary, only 59 of the one hundred and five coarctations seen at the Children's Memorial Hospital were amenable to excision and end-to-end anastomosis. Thirteen, in Types II-A and II-B, were infantile coarctations that were or could have been corrected by excision and standard replacement with aortic grafts or by utilizing the left subclavian artery to replace the excised aortic segment. Seven in Type IV were so distorted that surgical relief would have been impossible.

The twenty-six cases in Type III, however, had the infantile coarctation limited to the distal two-thirds of the aortic arch. Although they could not have been corrected by standard excision and homologous aortic graft replacement, they did have large ascending aortas, and aortic grafts could have been used to shunt the aortic stream around the coarctation into the descending thoracic aorta. In order to ascertain the technical feasibility of this procedure, a number of animal experiments were undertaken.

MATERIAL AND METHODS

Forty-three mongrel dogs were subjected to the proposed by-pass operation (Fig. 1). Free aortic grafts were taken from donor dogs and were preserved for two to six weeks by freezing. Prior to use, they were allowed to warm to room temperature. Their branches were carefully ligated and any tears in the walls were repaired by being sutured with 5-0 Deknatel arterial silk. Each graft was attached to the aorta of the recipient dog in the following manner. The chest was opened through the left fifth intercostal space. The descending thoracic aorta just distal to the left subclavian artery was dissected from its overlying mediastinal pleura and surrounding adventitia. It was not necessary to ligate any intercostal arteries. In addition, the pericardium was opened in the region of the ascending aorta at the base of the heart, and the fat pad located between the pulmonary artery and the ascending aorta was carefully removed by blunt and sharp dissection. A piece of umbilical tape was placed around the base of the ascending aorta to allow traction in case of emergency.

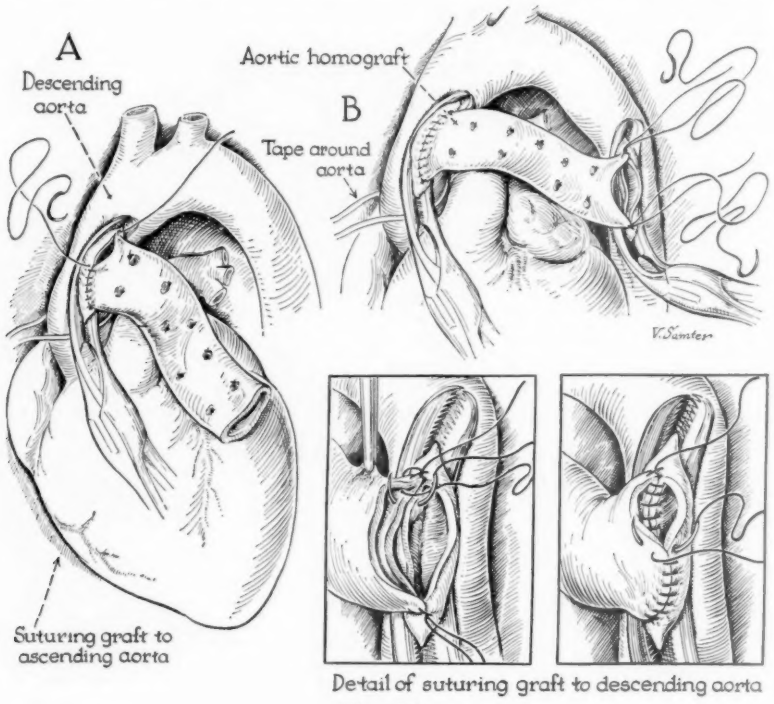


Fig. 3A.

Fig. 3.—Diagram of the proposed operation for long infantile coarctation of the aorta, as it was developed in the laboratory.

A curved coarctation clamp was applied to the anterolateral aspect of the base of the ascending aorta, parallel to the long axis of the vessel. Care was exercised not to interfere with the flow of blood from the left ventricle. A longitudinal incision was made in the wall of the ascending aorta within the coarctation clamp, and one end of the aortic graft was anastomosed to the sides of this incision with 5-0 Deknatel arterial silk. A continuous over-and-over noneverting suture technique was utilized. After completion of this anastomosis, with the coarctation clamp still in place, the graft was cut so that it would extend posteriorly around the pulmonary artery to the descending thoracic aorta without undue tension. Another curved coarctation clamp was applied to the descending aorta just distal to the left subclavian artery in such a manner that it occluded only partially the arterial stream. A longitudinal incision was made in the wall of the descending aorta within the coarctation clamp, and the other end of the aortic graft was anastomosed to this incision with a noneverting suture of 5-0 Deknatel arterial silk (Fig. 3).

After the ends of the aortic graft were securely fixed to the incisions in the ascending and descending aorta, the curved coarctation clamp on the descending aorta was released for a few moments to allow blood to flow into the homograft. This maneuver removed any air trapped within the graft and also provided blood for hemostasis at the suture lines. Within a few minutes, bleeding from the suture lines ceased and preparations were made for removing the curved coarctation clamps from the ascending and descending portions of the aorta.

Prior to release of the curved coarctation clamps, in order to simulate infantile coarctation of the aortic arch, a straight coarctation clamp was applied across the aorta at a point immediately below the left subclavian artery (Fig. 3, *C*). The distal curved coarctation was then released, filling the aortic graft with reflux blood from the descending aorta (Fig. 3, *D*).

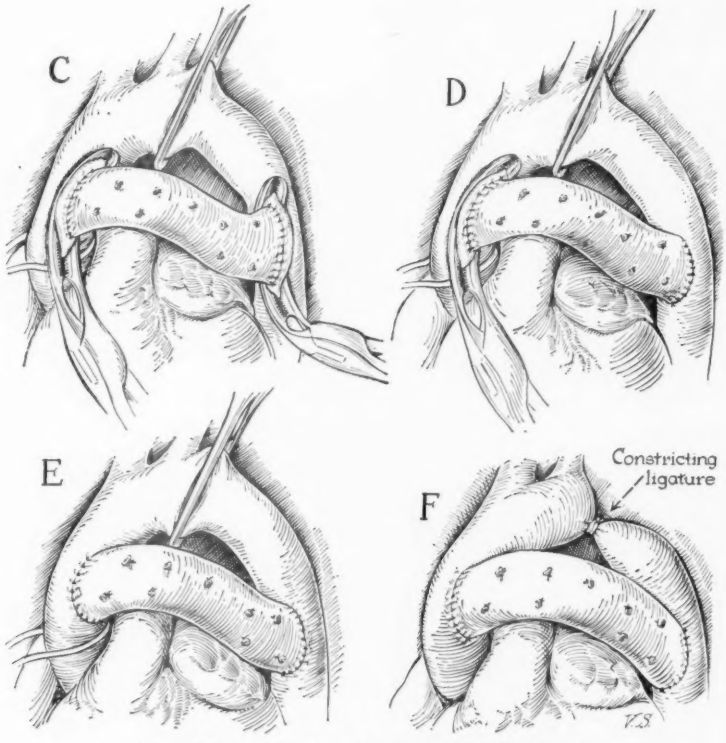


Fig. 3*B*.—*(For legend see opposite page.)*

As soon as hemostasis was certain, the curved coarctation clamp on the ascending aorta was opened, permitting the aortic stream to flow through the graft (Fig. 3, *E*). The straight coarctation clamp near the subclavian artery was then removed and was replaced by a stout ligature (Fig. 3, *F*). The animal's chest was closed and the animal was allowed to survive. During closure of the chest, it was noted that the aortic graft assumed a widely arched contour over the left pulmonary artery and left bronchus, permitting the lung to expand into the left hemithorax with impunity. The upper lobe and lingula of the left lung came into close contact with the graft, so that its revascularization was assured.

RESULTS

The results of these animal experiments may be divided into three groups.

Group I.—The first 17 animals were expended to develop the technical details of the procedure described. The operations were performed without blood

transfusion during surgery or antibiotics postoperatively. The immediate operative mortality amounted to 7 dogs (41.2 per cent). Most of these died of severe hemorrhage from the graft suture lines. Two died because of mild but uncontrollable hemorrhage, continuing after the aortic arch had been released and had retracted into the mediastinum. It became apparent that a piece of umbilical tape about the aortic base for traction was absolutely essential, until hemostasis was assured.

Ten dogs survived the operation, but 6 of these died within the first week postoperatively. One died of distemper. Autopsy revealed that the aortic homograft was functioning well. Three others died because the grafts became overdistended and ruptured. It became apparent that the aortic graft, in its frozen state, had to be at least the size of the descending thoracic aorta, in order to adequately carry the entire aortic stream. In fact, toward the end of this study, grafts larger than the ascending aorta were used. The only limiting factor to their size came to be the amount of aortic wall that could safely be included within the curved coarctation clamp at the base of the ascending aorta.

Two remaining dogs died from rupture of the aortic graft at the base of a ligated innominate artery stump. These two deaths discouraged the further use of segments of the aortic arch itself as homografts, because it was feared that the ligated stumps of the cephalic vessels were not revascularizing adequately.

Another important fact became obvious during these early endeavors. The ostium at the distal suture line of the aortic graft had to be large enough so that no obstruction to the blood flow through the graft could possibly exist. The incision in the descending thoracic aorta had to be made as long as or longer than, the incision in the ascending aorta.

Four dogs survived the immediate postoperative period and were sacrificed one to three months following surgery. In two of these, the shunt across the aortic graft was obligatory because a ligature had been placed around the aortic arch just distal to the left subclavian artery. In the other two, the aortic arch was left widely patent. The two latter grafts showed progressive narrowing of the lumina of their suture lines. In one, there was 40 per cent narrowing of the suture lines at post-mortem examination one month after operation. In the other, examined three months after operation, 90 per cent narrowing of the suture lines was observed. In the two dogs with obligatory shunts through the aortic grafts, the lumina of the suture lines were widely patent when examined one and three months postoperatively. It became apparent that, in the face of a nonobligatory shunt, the aortic graft would ultimately cease to function. This raised the question of whether or not the small channel, frequently present in infantile coarctations, should be entirely occluded by placing a ligature about the distal end of the coarctation. The question was answered later in the study when aortic arch ligatures in dogs used for longer observation were found slightly loosened by aortic pressure. This simulated the situation as it exists in human infantile coarctation. Since none of the grafts associated with small leaks across the aortic ligatures showed any sign of narrowing, it was felt that the distal end of human infantile coarctations would not have to be ligated.

Group II.—In the next group of 14 dogs, the proposed infantile coarctation operation was performed, using large homologous aortic grafts and making the shunt through the grafts obligatory. Blood transfusion was administered during and after surgery as indicated. There was no immediate operative mortality. However, because this group was not protected by antibiotics postoperatively, four dogs died of abscess formation within ten days to six weeks following surgery. Abscesses formed at the proximal suture line in two dogs and at the distal suture line in one. All three grafts ultimately ruptured at the site of the abscesses. A fourth dog developed infection at an intercostal ligature. This abscess finally eroded both aorta and lung, six weeks postoperatively, and the dog died of massive hemoptysis. The remaining ten dogs in this group survived beyond the immediate postoperative period and were sacrificed one to six months after operation.

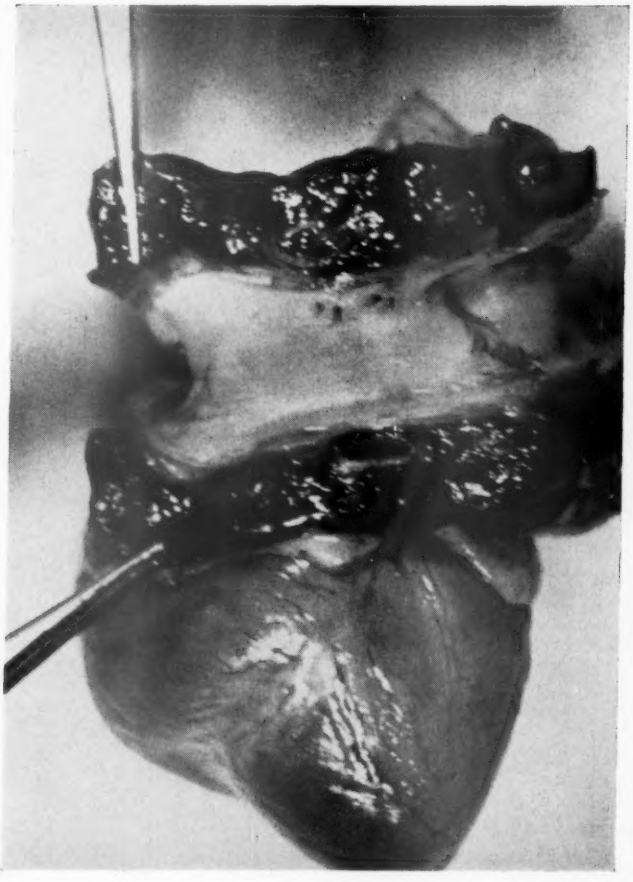
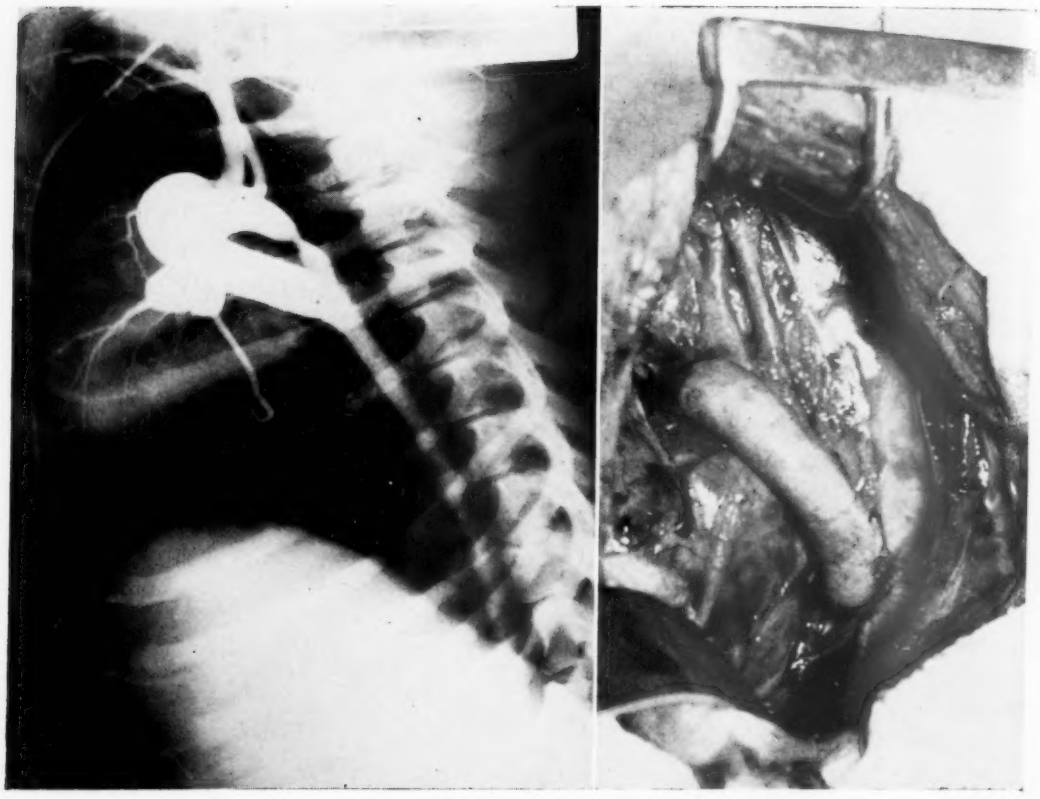
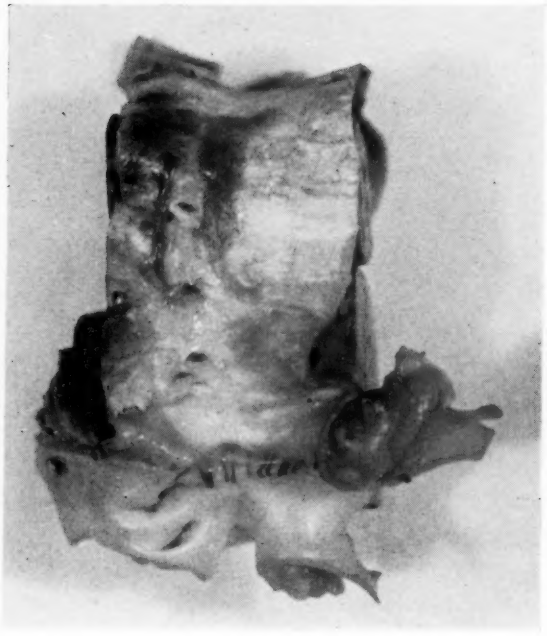


Fig. 4.—Gross appearance of an aortic graft three months after operation. Blood supply for the graft was derived to a large degree from the adjacent lung.

Group III.—The last group of twelve dogs were operated upon with careful attention to details of technique developed in the two previous groups and with adequate blood transfusion during and following operation. In addition, they received penicillin for twelve days postoperatively. There was no imme-



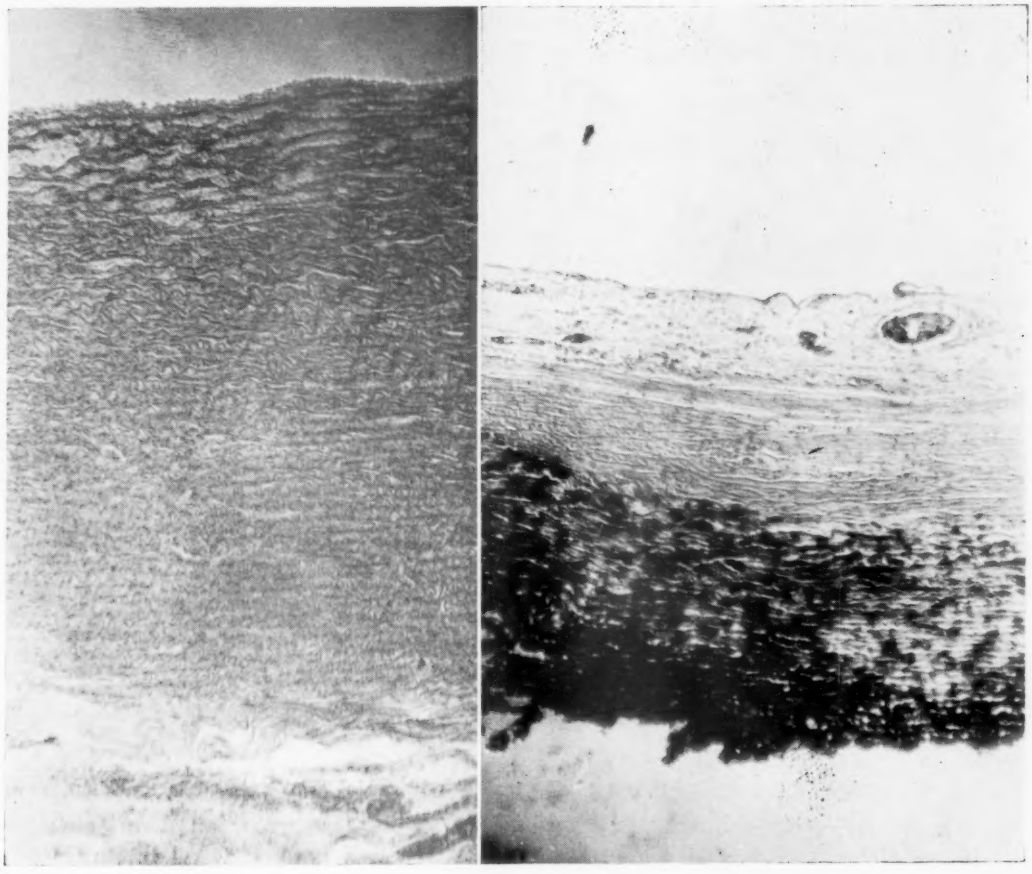
A. *B*



C.

Fig. 5.—*A*, Aortogram of a homologous aortic graft six months after operation. Note the constricting ligature at the distal end of the dog's aortic arch. The aortic graft arches over the left pulmonary artery. There is no aneurysm. *B*, Gross appearance of the same graft in situ. *C*, After sacrificing the animal, the graft shown in 5, *B* was opened to demonstrate the patent lumen, the well-epithelialized suture lines, and the furrowing of the intima.

diate or delayed operative mortality. The dogs have all done well and are being retained for long-range follow-up studies. Two of these dogs were puppies, weighing 9 pounds at the time of operation. Their operative weight has already tripled, yet pulsations of their femoral arteries continue to be prominent. Since they are expected to grow to six or seven times their operative weight by maturity, it is hoped they will provide some insight concerning the response of the aortic homografts to increased demands of growth.



A. *B.*

Fig. 6.—*A*, Comparative photomicrograph of a normal dog's aorta. *B*, Comparative photomicrograph of a homologous aortic graft six months after operation. The graft is thinner than the normal aorta and has calcium deposited in its tunica adventitia. The elastic tissue in the tunica media is compressed and fewer cell nuclei are visible.

POSTOPERATIVE STUDY OF THE AORTIC HOMOGRAFTS

A six-month postoperative follow-up has been completed on the dogs surviving in Groups I and II. Twelve dogs with obligatory shunts through homologous grafts were available. Two grafts were examined after one month, five were examined after three months, and five were examined after six months. All were widely patent and successfully carried the entire aortic stream around the obstruction produced in the distal aortic arch. All had been well revascularized by adhesions from the adjacent pericardium, pulmonary artery, and left

lung (Fig. 4). It was noted that calcium had been laid down in the walls of some of the older grafts, and their intimas showed evidence of furrowing. There was, however, no evidence of intimal destruction or aneurysmal dilatation (Figs. 5 and 6). These findings were not unlike observations recorded in other studies[10, 11] in which similar grafts have continued to function for many years. The dogs in Group III have been followed for periods up to nine months. They all have persistent femoral artery pulsations and appear to have no difficulties from their aortic homografts (Table II).

TABLE II. POSTOPERATIVE STUDY OF AORTIC HOMOGRAFTS IN 26 DOGS

Grafts with nonobligatory shunts	2
Fate: Closed within three months	
Grafts with obligatory shunts	24
Examined 1 month postoperatively	2
Examined 3 months postoperatively	5
Examined 6 months postoperatively	5
Retained for long-range follow-up	12
(All grafts widely patent and functioning satisfactorily)	

SUMMARY

1. Review of one hundred and five patients with coarctation of the aorta entering the Children's Memorial Hospital indicates that at least 21.9 per cent have infantile coarctation of the distal two-thirds of the aortic arch, without involvement of the ascending aorta and without other serious congenital anomalies. These cases have not been amenable to surgery in the past.

2. It is proposed that, in such cases, relief be obtained by using a homologous aortic graft to connect the ascending aorta with the descending thoracic aorta distal to the coarctation, without attempting to excise the narrowed segment of the aortic arch.

3. Forty-three mongrel dogs were used to develop the technical aspects of the proposed operation. These experiments are described and the results are listed.

4. The last twelve dogs have been operated upon without any immediate or delayed operative mortality. Two of these operations were performed on newborn puppies weighing 9 pounds.

5. A six-month study on the homologous aortic grafts in the surviving dogs indicated that the grafts are performing well and that the operation is feasible in human beings.

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THE RELATIONSHIP OF CORONARY BLOOD FLOW AND CARDIAC OUTPUT AND OTHER PARAMETERS IN HYPOTHERMIA

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CORONARY blood flow in the hypothermic animal is dependent upon two groups of opposing influences. The factors which tend to reduce flow include diminished cardiac output, reduced arterial pressure, increased blood viscosity, hemoconcentration, and the increased duration of the systolic phase of ventricular contraction.[1-5] Opposing these factors are the possible relaxation of the major coronary vessels and dilatation of the coronary bed.[6-9] The material in this study primarily concerns the relationship of coronary flow, as measured by a direct-recording rotameter, to cardiac output, determined by the dye-dilution method. In order to define better the physiologic status of each animal and to assess more accurately the changes occuring in the coronary circuit, other related parameters were also studied.

METHOD

Hypothermia was induced in 13 adult mongrel dogs. Pentothal sodium was administered intravenously (30 to 40 mg. per kilogram) and was discontinued after cooling had begun, in order to minimize the effects of anesthesia. An endotracheal tube was passed, securely tied in place, and connected to a respirator (pneophore) supplied with oxygen. The left chest was entered through the fourth intercostal space and the pericardium was opened. The circumflex branch of the left coronary artery was dissected free for a distance of approximately 1 cm. at its origin. The animal was then given 100 mg. of heparin; an additional 50 mg. was given each thirty minutes thereafter to prevent fibrin deposition within the rotameter. The left carotid artery was used as the source of blood for the rotameter.[10] A small cannula leading from the rotameter was placed in the distal portion of the circumflex artery, and the proximal portion of the vessel was ligated. Coronary flow was recorded optically and frequent zero readings were taken to ensure the accuracy of the measurements. A diagrammatic illustration of the experiment as performed is shown in Fig. 1.

Total body oxygen consumption was determined by connecting the endotracheal tube to an oxygen-filled modified spirometer which could be driven as a positive-pressure respirator. Carbon dioxide was removed by a cannister of soda lime. Tidal volume was controlled by visual inspection of the lungs in the opened chest. Cardiac output was determined by the dye-dilution method using a cuvette densitometer.[11, 12] Dye was injected through a small polyethylene catheter inserted in the external jugular vein and passed into the superior vena cava. A carotid artery was cannulated and connected by polyethylene tubing to the cuvette of the densitometer. Mean arterial pressure was determined by a mercury manometer from a carotid artery, and in some instances phasic pressure curves were recorded using a Statham

Received for publication Jan. 19, 1955.

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strain gauge. Venous pressure was measured with a saline manometer through a polyethylene catheter passed into the superior vena cava. The circulation time was determined with a stop watch from the instant dye was injected into the superior vena cava to the beginning of its appearance in the carotid artery as recorded by the densitometer. All blood withdrawn was immediately replaced with an equal amount from a donor.

Control determinations were made for each of the parameters described, and hypothermia was then induced by means of direct cooling of the blood accomplished by interposing a brass coil (4 mm. in diameter and 180 cm. in length) between the femoral artery and femoral vein. The coil was immersed in an ice bath at 0° to 4° C. At normal body temperature the amount of blood flow through this coil was 80 to 160 c.c. per minute. The pressure drop through this system was such that no effects on hemodynamics due to an arteriovenous shunt were perceptible. Nevertheless, the circuit was clamped off for one minute prior to each determination. Temperature was recorded by a rectal thermometer. In the group in which comparisons of coronary flow and cardiac output were made, the time from the onset of hypothermia until a temperature of 25° C. was reached averaged eighty-seven minutes.

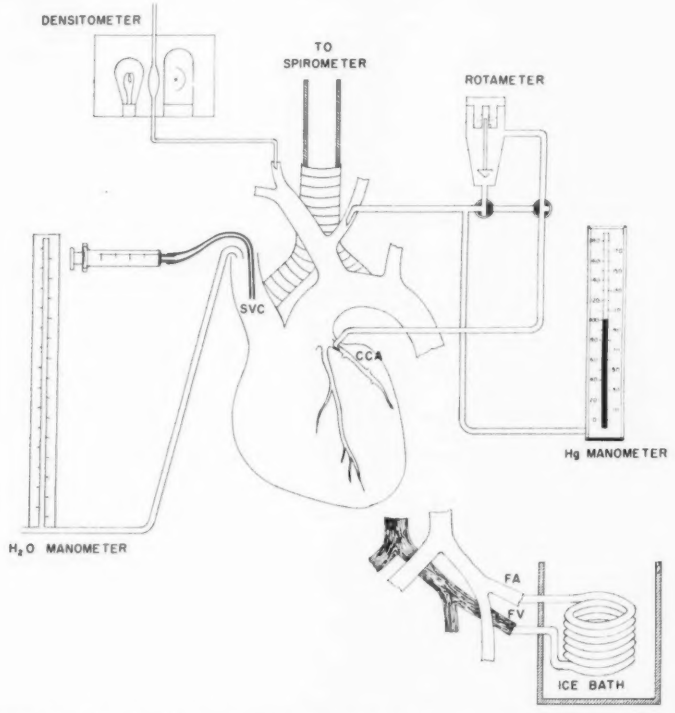

Fig. 1.—Diagrammatic illustration of experiment as performed. *CCA*, Circumflex coronary artery; *SVC*, Superior vena cava; *FA*, femoral artery; *FV*, femoral vein.

In order to assess the influence of the thoracotomy and the various studies per se upon the preparation without hypothermia, an additional six animals were subjected to a left thoracotomy with insertion of a coronary cannula just as those in the hypothermic group, and the various parameters were determined over a two-hour period. The results obtained from these preparations gave control data in addition to the control studies made prior to the onset of hypothermia in that group.

RESULTS

With the lowering of body temperature, a depression occurred in each of the parameters studied. The data from a typical experiment are shown in Fig. 2. In this instance the temperature was lowered from 39° C. to 24° C., and all of

the measured parameters fell considerably. The average initial and final values of each parameter studied in the hypothermic and control experiments are shown graphically in Fig. 3. For the hypothermic group the average fall in temperature was 14° C. Oxygen consumption fell from an average of 168 to 52 c.c. per minute per square meter, representing a reduction of 69 per cent or a 5 per cent decrease for each degree centigrade. Heart rate fell steadily from an average of 146 to 62 (56 per cent). Mean arterial pressure was reduced from

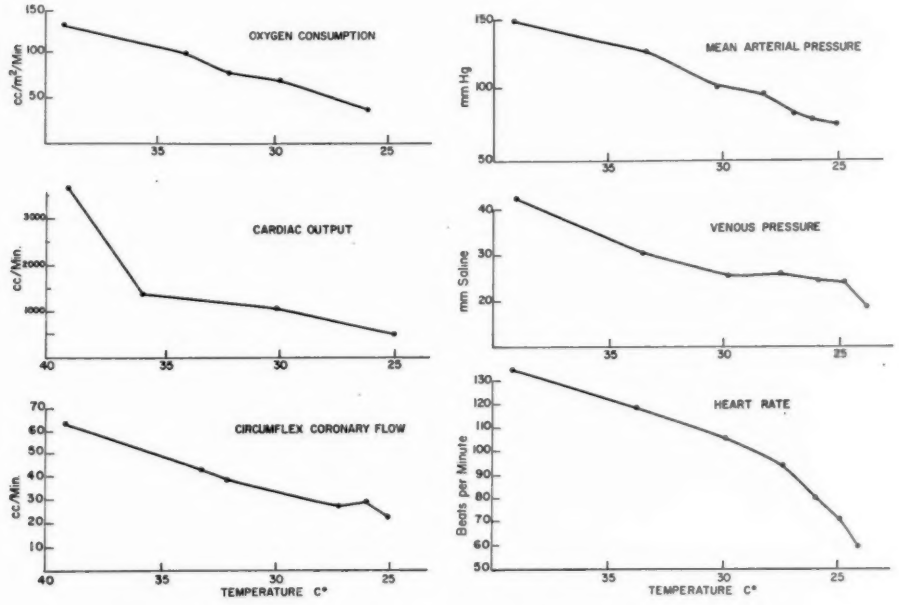

Fig. 2.—Data from typical experiment (dog weight 21.8 kg.).

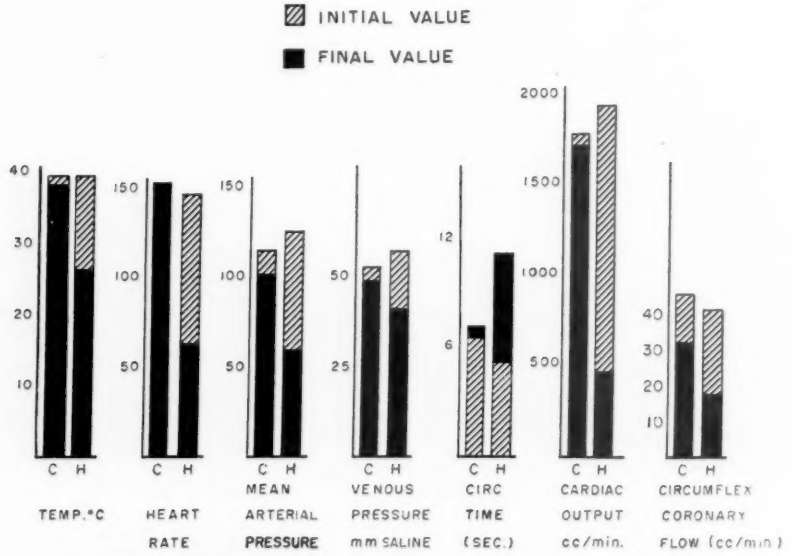

Fig. 3.—Data from control and hypothermic preparations. *C*, Control animals with initial determination and at two hours; *H*, hypothermic animals with initial determination prior to onset of hypothermia and final value at 25° C.

an average level of 123 to 58 mm. Hg. Further analysis of this depression showed that the pressure was frequently well maintained during the early stages of hypothermia but fell more sharply between 30° C. and 25° C. There was only a moderate decrease in the venous pressure with a drop from a control of 56 to 40 mm. of saline solution. Further evidence of a hypodynamic circulation was reflected in the circulation time which rose from a control of five seconds to eleven seconds (208 per cent). During this time a marked reduction occurred in cardiac output with a fall from a control value of 2,264 c.c. per minute to 575 c.c. per minute, representing a decrease of 75 per cent (Fig. 4).

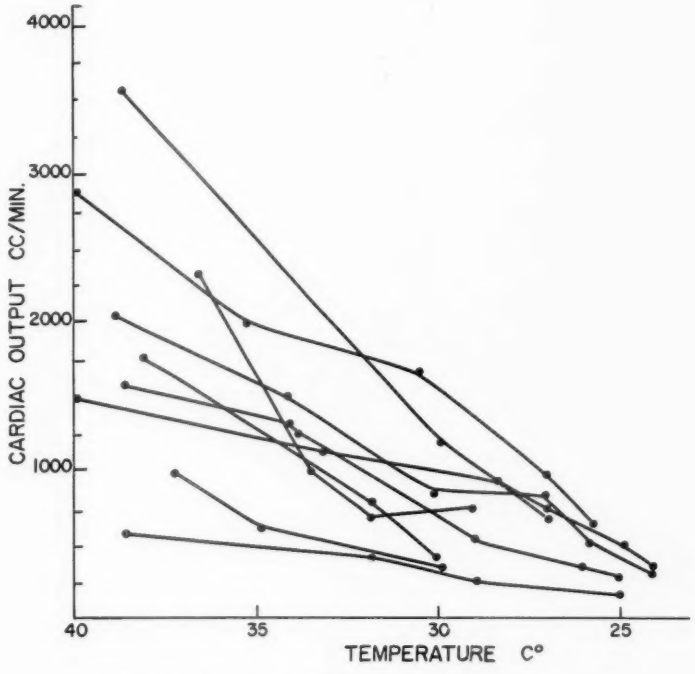

Fig. 4.—Effect of hypothermia on cardiac output.

Coronary blood flow was determined in ten animals and a reduction of flow occurred in each instance. The fall is illustrated in Fig. 5. The average value for circumflex coronary flow before hypothermia was 47.2 c.c. per minute; this fell to 20.1 c.c. per minute at 25° C., or to 42.6 per cent of the control value. In six of these animals, concomitant determinations of cardiac output were made. In this group the average control circumflex flow was 38.3 c.c. per minute, with a drop to 15.8 per minute, or 42.1 per cent of the original value. In the control state the circumflex coronary flow represented 1.8 per cent of the total cardiac output (38.3 c.c. per minute over 2,264 c.c. per minute) as compared with 2.9 per cent at a temperature of 25° to 26° C. (15.8 c.c. per minute over 575.3 c.c. per minute). This increase in the coronary fraction of cardiac output occurred in each animal (Table I). Although the absolute coronary flow is decreased at low temperatures, the myocardium receives a larger fraction of the cardiac output than at normal body temperature.

A comparison of the data obtained in the control group with those of the experimental group further confirms the concept that these alterations are the result of hypothermia. The control preparations maintained a reasonably steady state throughout the two-hour period of observations. The changes which occurred were small, as a rule. Coronary flow was reduced 28.8 per cent at the

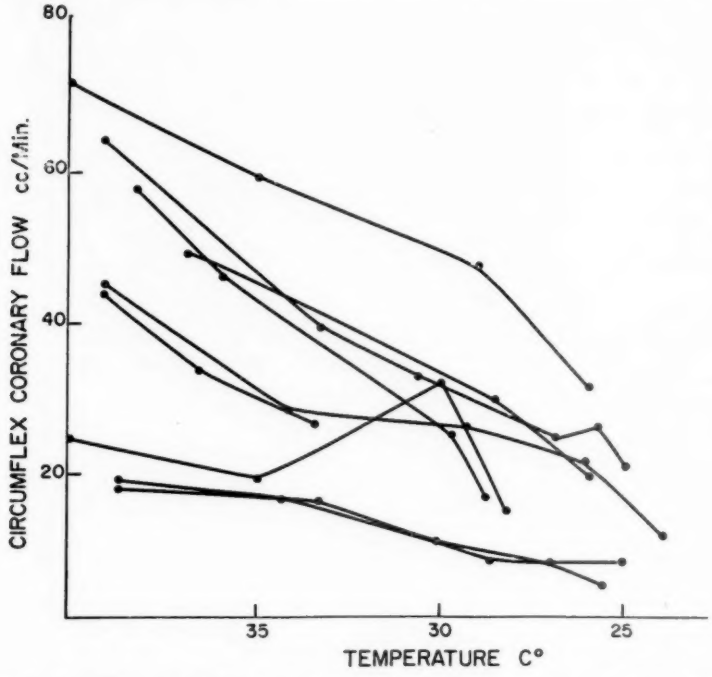

Fig. 5.—Effect of hypothermia on circumflex coronary artery flow.

end of two hours; however, most of this reduction occurred toward the end of the period. At a time comparable to that of the average experiment in the hypothermic group (87 minutes), the average decrease in flow was 11 per cent. Cardiac output at the end of two hours was reduced 5.2 per cent, resulting in a 13 per cent decrease in blood flowing through the coronary circuit as compared with the cardiac output. In other words, this represents an opposite directional trend from that found in hypothermia.

DISCUSSION

In 1929, Anrep, Blalock, and Hammouda,[13] using the heart-lung preparation, demonstrated that coronary flow increased when the coronary circuit was perfused with blood at low temperatures. Similar results were also obtained by Markwalder and Starling[14] and Nakagawa.[8] Cruickshank[6] has shown that isolated rings of coronary artery are relaxed at 25° C., and that they contract as the temperature rises from 27° C. to 38° C. In contrast, rings of other systemic arteries (carotid, renal, mesenteric, and femoral) contract with cooling and relax with warming. These responses may be held as evidence that the coronary system responds to the stimulus of lowered temperature with mechanisms which tends to increase flow through the myocardial bed.

Recent studies on the response of the cardiovascular system to general hypothermia indicate that changes occur which tend to decrease blood flow through vascular beds. Hegnauer and associates[2] are responsible for much of the data now available on this subject. They noted that total body oxygen consumption and cardiac output fall to 15 per cent, respectively, at 17° C. In other studies they found that mean arterial pressure and heart rate also fell,[1] and that there is a tendency toward hemoconcentration as evidenced by a rising hematocrit.[3] Specific determination of blood viscosity revealed a two- to threefold increase at a temperature of 20° C.[1] Studies of ventricular contraction have been made by Berne[4] who found that the period of ventricular systole was greatly lengthened during hypothermia. Each of these factors tends to result in a decrease in coronary blood flow.

The volume of blood flowing through the coronary circuit is thus determined by the relative influence of each of the foregoing factors in augmenting or reducing the flow through the bed. The data obtained in the present study indicate that circumflex coronary flow is considerably reduced at low temperatures. However, the reduction in cardiac output is greater, which results in an increase in the coronary fraction of cardiac output. The mechanism by which this increase occurs cannot be stated with certainty. In a recent study by Berne on coronary flow in hypothermia, it was concluded that coronary resistance was reduced since artificial elevation of coronary perfusion pressure yielded flows greater than those obtained at identical pressures in the control and early stages of hypothermia. However, the values for coronary resistance as calculated by the ratio of mean arterial pressure and coronary flow demonstrated a rise when the coronary bed was perfused at low temperature at the prevailing aortic pressure. In the present studies, this ratio did not change appreciably in the coronary bed during hypothermia and was calculated to be 4.1 for the control value and 4.2 at 25° C. (mean arterial pressure mm. Hg per circumflex coronary blood flow c.c. per minute). In the control experiments without hypothermia, there also was essentially no change, with an initial value of 2.5 and a final value of 2.6. However, a definite change occurred in the calculated resistance in the systemic bed in the hypothermic group with a control value of 6.1 and a value of 10.8 at 25° C. (mean arterial pressure mm. Hg times 100 per cardiac output c.c. per minute). No appreciable change occurred in the systemic resistance in the group without hypothermia with initial and final values of 6.5 and 5.9, respectively. These figures suggest that in hypothermia there is little change in the peripheral resistance in the coronary bed, whereas there is an increase in the peripheral resistance in the remainder of the systemic bed. Furthermore, the values obtained in the control group without hypothermia indicate that the procedure itself does not appreciably alter peripheral resistance.

Coronary flow in the hypothermic, closed-chest dog has recently been studied by Edwards and co-workers,[15] using the nitrous oxide technique. In their animals coronary flow was reduced at low temperatures, and calculations from their data indicate that the coronary fraction of the cardiac output was increased over the control state. Their findings support the data presented here which indicate

TABLE I. EFFECT OF HYPOTHERMIA ON CARDIAC OUTPUT, CORONARY FLOW, AND MEAN ARTERIAL PRESSURE*

		CONTROL				HYPOTHERMIA (25° TO 26° C.)						
DOG NO.	WT. (KG.)	C.O. (C.C./ MIN.)	M.A.P. (MM. HG)	C.C.F. (C.C./ MIN.)	PER CENT OF C.O.	C.O. (C.C./ MIN.)	PER CENT OF CONTROL C.O.	M.A.P (MM. HG)	C.C.F. (C.C./ MIN.)	PER CENT OF CONTROL C.C.F.	PER CENT OF C.O.	PER CENT INCREASE IN CORONARY FRACTION OF C.O.
1	13.6	1,590	108	45.5	2.86	488	30.7	64	22.0	48.3	4.51	58
2	12.3	2,180	126	19.5	0.89	500	22.9	44	6.5	33.3	1.30	46
3	14.5	1,510	140	18.5	1.23	375	24.9	61	8.5	45.9	2.27	85
4	14.1	1,760	120	57.0	3.24	450	25.6	48	18.5	32.5	4.11	27
5	14.5	2,896	106	25.0	0.86	973	33.6	52	13.0	52.0	1.34	56
6	21.8	3,650	150	64.0	1.75	666	18.2	64	26.0	40.6	3.90	123
Average		2,264	125	38.3	1.8	575	25.0	56	15.8	42.1	2.9	66

C.O.—Cardiac output.
M.A.P.—Mean arterial pressure.
C.C.F.—Circumflex coronary flow.
*Animals in this group had concomitant measurements of cardiac output, circumflex coronary flow, and mean arterial pressure.

that coronary blood flow is reduced at low temperatures, although comparison with the low values for cardiac output indicates that the coronary fraction of cardiac output is increased.

SUMMARY

Observations have been made on a group of dogs during hypothermia induced by direct blood cooling. Simultaneous measurements of cardiac output, oxygen consumption, mean arterial pressure, heart rate, and venous pressure have been determined. Moderate to marked reduction in each of these parameters has been found. Circumflex coronary flow is also reduced. However, the percentage reduction in cardiac output is greater than in coronary flow which results in an increase in the coronary fraction of cardiac output at temperatures of 25° to 26° C.

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THE EFFECT OF HYPOTHERMIA ON THE OUTPUT OF 17-HYDROXYCORTICOIDS FROM THE ADRENAL VEIN IN THE DOG

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ALTHOUGH a few experiments on the pituitary-adrenal response to stress in hypothermia have been reported,[1, 2] precise data on the adrenocortical hormone output during body cooling are not available. This report concerns a study of the output of 17-hydroxycorticoids from the adrenal vein in the hypothermic animal. This investigation was undertaken to determine the functional state of the adrenal cortex and its response to stress before, during, and after hypothermia.

EXPERIMENTAL METHOD

Eight adult male mongrel dogs weighing 14 to 21 kilograms were used. Anesthesia was induced with pentobarbital sodium and maintained with ether, utilizing a positive pressure apparatus. The right adrenal gland was exposed and the right lumboadrenal vein cannulated, using the technique of Hume and Nelson.[3] A plastic cord was passed around the lumboadrenal vein between the adrenal gland and the entrance of the lumboadrenal vein into the inferior vena cava. The two ends of the cord were then passed through a piece of plastic tubing, producing a snare. By tightening or loosening the snare, intermittent interruption of the lumboadrenal vein flow could be produced. The lumboadrenal vein then was ligated distal to the adrenal gland and all branches proximal to the ligature were interrupted. A polyvinyl cannula was inserted through the vein to the adrenal permitting retrograde flow of all adrenal venous blood when the snare was tightened. Finally, the snare and cannula were led to the exterior and the incision closed. During the interval between samples, the cannula was filled with heparin–saline solution and the snare released so that adrenal blood flowed normally into the inferior vena cava.

Continuous blood pressure recordings were obtained from the femoral artery with a U-tube mercury manometer. The other femoral artery and a femoral vein were cannulated to obtain arterial blood samples and to permit intravenous injection of ACTH.

This study was supported in part by a grant-in-aid from the Commonwealth Fund and by the Committee on Metabolism in Trauma, Commission on Liver Diseases, Armed Forces Epidemiological Board, and supported by the Surgeon General, Department of the Army, through a contract (DA-49-007-MD-472) with Harvard University Medical School. The generous assistance of the Samuel Cabot Fund is also gratefully acknowledged.

Received for publication March 7, 1955.

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The dogs were cooled by immersion in an ice-water bath maintained at 3° C. Temperature was recorded with an esophageal thermocouple and rectal thermometer. When the animal's temperature reached 27° C., it was removed from the bath, and the temperature was permitted to drift downward to a range of 26 to 24° C. Rewarming was accomplished by immersion in a warm-water bath at 45° C.

Adrenal venous blood was collected directly into heparinized, graduated test tubes and the blood flow per minute recorded. All samples were centrifuged within three hours and the plasma stored in a frozen state. The plasma 17-hydroxycorticoids were determined by the method of Silber and Porter,[4] and the output was calculated in gammas per minute, assuming a hematocrit of 50 per cent. Samples were taken according to the protocol listed in Table I. The first was obtained immediately after the flank wound had been closed. The response to ACTH was then tested by injecting 10 milliunits of USP Reference Standard ACTH dissolved in 10 c.c. of 0.01 normal hydrochloric acid in saline solution. After the induction of hypothermia, a standard operative stress was performed consisting of exposure of the right sciatic nerve. A second intravenous dose of ACTH was then administered, and the animals were rewarmed.

TABLE I. SCHEDULE FOR SAMPLING OF ADRENAL VENOUS BLOOD

PHYSIOLOGIC STATE	TEMPERATURE (° C.)	COLLECTION PERIOD (MIN.)
1. Stressed by adrenal vein cannulation	37	3-5
2. Three minutes following intravenous ACTH	37	5
3. Hypothermia—cooling	30	5
4. Hypothermia	24-26	10-15
5. Hypothermia—five minutes after standard operation (second stress)	24-26	10-15
6. Three minutes following intravenous ACTH	24-26	10-15
7. Hypothermia—rewarming	30	5-10
8. Rewarmed	37	3-5

In five of the animals, hypovolemic shock was produced in order to compare the altered physiology of hypothermia with another situation producing reduced adrenal blood flow. The animals were bled into plastic bags until the mean systolic blood pressure dropped to 45 mm. Hg. After stabilization at this level, adrenal venous samples were taken and retransfusion carried out immediately. In four dogs, this procedure was carried out before cooling, and in a fifth dog, after rewarming.

RESULTS

Surgical Operation and ACTH Stimulation.—The mean adrenal blood flow, corticoid concentration, and corticoid output for eight dogs are recorded with accompanying changes in temperature and blood pressure in Fig. 1. These data are remarkably constant from dog to dog. Mean adrenal blood flow at the time of the first sample was 5.0 ± 0.4 c.c. per minute.* Plasma corticoid concentration was 3.5 ± 0.4 gamma per cubic centimeter, resulting in a corticoid output of 8.6 ± 0.7 gamma per minute. This output is the maximum which the

*Standard error of the mean.

normal adrenal gland can produce, as shown by the absence of a significant rise after ACTH administration (mean corticoid output value 8.9 ± 1.0 gamma per minute). Cooling of the animal to 30° C. produced a small drop in adrenal blood flow (3.2 ± 0.3 c.c. per minute) and hence, a fall in corticoid output (5.0 ± 0.8 gamma per minute). At a mean temperature of 24° C., adrenal blood flow had fallen to 1.2 ± 0.3 c.c. per minute without a significant rise in corticoid concentration, resulting in a fall in adrenal corticoid output (2.0 ± 0.4 gamma per

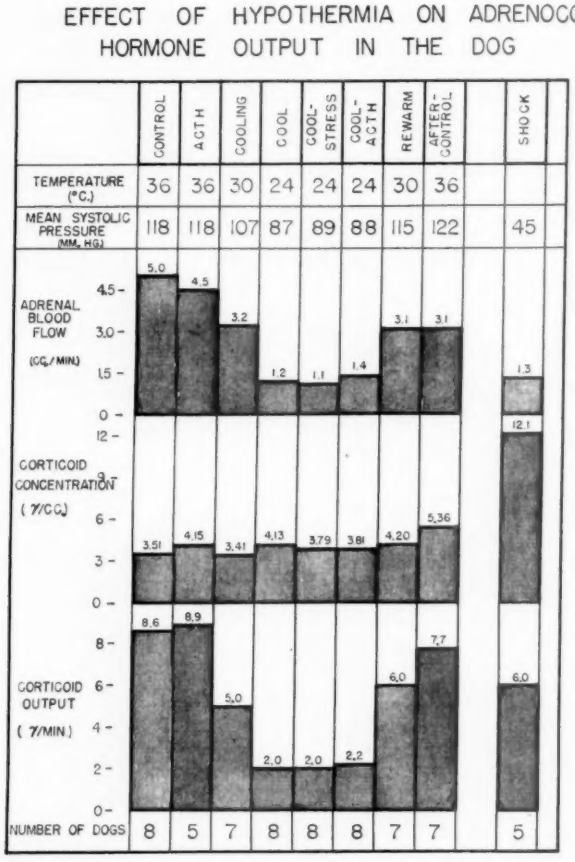


Fig. 1.—Graph of adrenal blood flow, 17-hydroxycorticoid concentration, and corticoid output in dogs subjected to hypothermia and shock. The column marked "Number of Dogs" represents the number of animals on which values were obtained and averaged to give the charted values in each vertical column.

minute). With additional surgical stress during hypothermia, this value did not increase; the mean output remained at 2.0 ± 0.3 gamma per minute. Furthermore, the output did not change appreciably after ACTH stimulation (2.2 ± 0.2 gamma per minute). When the animal had rewarmed to 30° C., adrenal flow and concentration increased, resulting in a corticoid output of 6.0 ± 0.9 gamma per minute. After restoration to a normal temperature, corticoid output returned to the precooling level. At the termination of the experiment, blood flow in some dogs did not reach the prehypothermic level, the mean flow being 3.1 ± 0.3 c.c. per minute. However, unlike the situation during hypothermia, these

animals were able to increase the concentration of corticoids in the adrenal venous blood. Thus, the mean concentration was 5.36 ± 1.1 gamma per c.c., and the resultant mean output 7.7 ± 6.3 gamma per minute, a result similar to the values obtained at the start of the experiment.

Hemorrhagic Shock.—Mean values obtained in the five animals subjected to hemorrhagic shock and subsequent retransfusion showed a prompt fall in adrenal blood flow from a stressed normal level of 5.0 ± 0.4 c.c. per minute to 1.3 ± 0.5 c.c. per minute. At the same time, there was a rise in corticoid concentration from 3.51 ± 0.4 gamma per cubic centimeter to 12.10 ± 2.7 gamma per cubic centimeter. Adrenocortical hormone output per minute was thus maintained at the preshock level. This ability of an adrenal gland to raise corticoid concentration with a fall in adrenal blood flow produced by shock was present not only in the four animals bled before cooling but also in the one animal bled after rewarming. In the latter dog, corticoid concentration rose from 2.53 gamma per cubic centimeter before, to 9.07 gamma per cubic centimeter during shock. In addition, another animal developed shock secondary to wound hemorrhage during rewarming. Even when incompletely rewarmed (30° C.), this dog responded with a rise in corticoid concentration to 8.73 gamma per cubic centimeter.

DISCUSSION

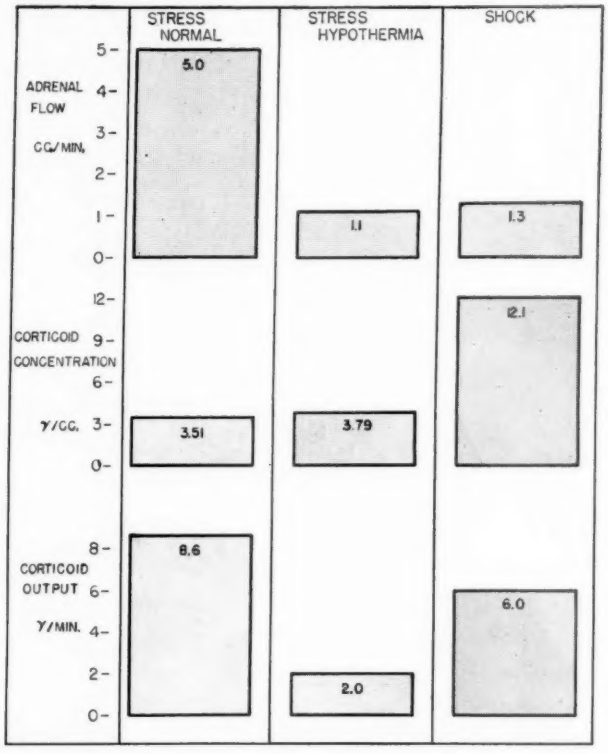
It must be remembered that adrenal venous cannulation constitutes a major stress to the animal and, therefore, all values for adrenal corticoid output obtained in this experiment are from the maximally stimulated adrenal gland. This is confirmed by the absence of an increase in output after the administration of ACTH.

The dose of ACTH used is intentionally small to produce a short-term stimulation of the adrenal gland. Studies of the hypophysectomized dog in this laboratory have established that 10 milliunits of ACTH produce a maximal adrenocortical stimulation about three minutes after injection and that this effect is dissipated within forty minutes.[5, 6]

To demonstrate that the decrease in adrenal cortical hormone output observed with cooling was not due simply to a diminution in the magnitude of the initial stress, the animals were subjected to further stress (surgery) after cooling to 26 to 24° C. This failed to produce any rise in corticoid minute output. To rule out a fall in hormone output on the basis of a decrease in the amount of circulating ACTH, exogenous ACTH was administered, with no subsequent change in corticoid output.

Khalil has reported that the adrenal is responsive to ACTH stimulation during hypothermia.[1] However, his data are based on the ascorbic acid fall in the rat, and his results demonstrated a response of low magnitude. In contrast to that report, this experiment indicates that the adrenal gland in the hypothermic animal is not responsive to increases in the amount of circulating ACTH. This indicates that the corticoid output of 2.2 gamma per minute is the maximum of which the adrenal is capable in a hypothermic animal.[7] It should be emphasized that these data do not rule out an associated decrease in the secretion of ACTH during hypothermia.

The data from the five dogs subjected to shock revealed a fall in adrenal blood flow to the same level observed during hypothermia. However, at normal temperature, there was an associated marked rise in the concentration of 17-hydroxycorticoids. Therefore, the total hormone output remained at or near preshock levels. This confirmed the work of others who found a similar rise in concentration associated with a fall in flow during shock.[3, 8, 9] There is evidence of a critical level of adrenal blood flow, probably in the range of 10 to 15 per cent of normal, below which it is impossible for the adrenal to maintain normal cortical hormone output.[8] In the present experiments, flow was not reduced to



EFFECT OF SURGICAL TRAUMA ON ADRENOCORTICAL HORMONE OUTPUT IN THE DOG

Fig. 2.—The values are means obtained from the dogs in the present study and are taken from Fig. 1. They are charted individually to permit comparison of the effect of stress in the normal dog, in the hypothermic dog, and in the presence of hypovolemic shock on adrenal blood flow and 17-hydroxycorticoid output.

this level, indicating an associated depression of the adrenal capacity to secrete 17-hydroxycorticoids (Fig. 2). Furthermore, the shock studies tend to rule out the fall in blood pressure associated with hypothermia per se as the cause of the decrease in adrenocortical function. The mean pressure of these dogs fell from a control level of 118 mm. Hg to 87 mm. Hg when the body temperature was 24° C. On the other hand, a blood pressure of 45 mm. Hg was not associated with a fall in corticoid output when body temperature was normal.

The output of 17-hydroxycorticoids per minute before cooling in the dogs of the present series agrees well with the range of normal values obtained by

Hechter,[8] who used a different chemical method. They are consistently lower than those of Hume and Nelson,[3] but these investigators also employed a different method of chemical analysis and performed their analyses on whole blood. Thus, the latter series are not strictly comparable with the present data.

The practical significance to the organism of reduction in adrenal cortical hormone secretion during hypothermia is speculative. At any rate, with rewarming, normal adrenocortical function returns promptly, permitting the full gamut of adrenal-dependent metabolic adjustments of stress to occur. Tissue metabolism and blood flow are decreased with hypothermia and one might expect tissue hormone demands to be lowered. It is known that hypothermia depresses hepatic[10, 11] function; this may well slow down conjugation of the free cortical hormones.[12, 13] Therefore, a diminished rate of hormone destruction may balance the decrease in production, allowing the level of the active hormone presented to the tissues to be higher than expected from secretion data alone. Studies of peripheral arterial 17-hydroxycorticoid levels during hypothermia will be interesting in this respect, and are now in progress in this laboratory.

These animals were subjected to operative trauma before as well as during hypothermia. This is not entirely different from the surgical patient because both anesthesia[14] and cooling[1] are mild stresses. These would tend to produce a slight rise in adrenal hormone secretion before the depression due to hypothermia manifested itself.

SUMMARY

1. Eight dogs were prepared by cannulation of the right adrenal vein, and hypothermia produced by surface cooling. Adrenal blood flow and 17-hydroxycorticoid output were determined before, during, and after cooling. The responses to ACTH and surgery were determined before and during cooling. In five dogs, hemorrhagic shock was induced and adrenal venous samples collected to compare the effects of shock with those of hypothermia.

2. Hypothermia is associated with a decrease in adrenal blood flow and a fall in 17-hydroxycorticoid output.

3. The low adrenal cortical hormone output in hypothermia is not altered by additional surgical stress or the injection of ACTH.

4. Normal adrenal blood flow and 17-hydroxycorticoid output return promptly with rewarming.

5. Hemorrhagic shock in an animal at normal body temperature produces a marked reduction in adrenal blood flow and an associated rise in corticoid concentration in the adrenal venous blood. Total corticoid output does not fall.

6. It is concluded that there is a specific depression of adrenocortical hormone secretion during hypothermia.

Acknowledgments.—Special thanks are due Miss Hildegarde Junker and Miss Margaret Hanley for technical assistance.

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DOES UNCOMPLICATED PLEUROPERICARDIOMEDIASTINITIS RESULT IN MYOCARDIAL HYPERTROPHY?

An Experimental Study

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THE following experimental study was undertaken for the purpose of determining whether or not pleuropericardiomediastinitis causes cardiac hypertrophy. Some divergence of opinion, based for the most part on clinical evidence, is found in the medical literature. Most observations discussing cardiac hypertrophy in relation to pericarditis do not clearly differentiate the type of pericarditis. Three distinct varieties of pericarditis are recognized:

1. Chronic adhesive pericarditis in which the two layers of pericardium are bound together, thus obliterating, either partially or completely, the pericardial sac. These patients often have no cardiac hypertrophy or embarrassment.

2. Chronic constrictive pericarditis, formerly called Pick's disease, in which there is marked fibrous thickening and often calcification of the pericardium. This frequently interferes with cardiac action, either by direct cardiac constriction or by narrowing the orifices of the venae cavae, thus diminishing the cardiac output.

3. Mediastinopericarditis in which the parietal pericardium is firmly bound to adjacent structures by fibrous adhesions. Uncomplicated mediastinopericarditis does not include adhesions between the epicardium and parietal pericardium, but involves only the parietal pericardium and mediastinum, pleurae, and diaphragm. In theory, this should result in no increase in the work demanded of the myocardium and, therefore, hypertrophy would not result.

HISTORICAL REVIEW

Observations made prior to 1920 made little differentiation between the three types of pericarditis described here. The first clear description of pericarditis in the medical literature was given by White in 1669. Lincisi, in 1728, and Laennec, in 1819, later described the same disease. In 1761, Morgagni stated that adherent pericardium led to absence or weakness of the apex beat, edema, and ascites. He apparently referred to the constrictive type of pericarditis even though he did not make reference to any specific anatomic findings. In 1842, Chevers discussed the relationship of pericarditis to cardiac

Received for publication March 17, 1955.

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enlargement and concluded that enlargement of the heart occurred only when there was associated valvular damage. He reported that some of his patients showed mediastinal adhesions only and in these cases the heart was of normal size.

Other writers offered the opposite view, namely, that pericarditis could produce hypertrophy of the heart. Hope, in 1832, and Broadbent, in 1895, emphasized this view, leading to the impression that cardiac enlargement was the most important, if not the only, effect of adherent pericardium.

Occasional experimental studies attempting to establish a relationship between pericarditis and cardiac hypertrophy may be found in the literature. Volhard, in 1923, and Beck, in 1929 and 1937, produced constrictive pericarditis experimentally. Their animals developed signs of heart failure but the heart was small and quiet. Herrmann and Musser, on the other hand, in 1927, reported that experimentally produced adhesive pericarditis in dogs resulted in considerable hypertrophy of the heart and attributed this to the increased work placed upon the heart. Although they did not specifically mention adhesions between both layers of the pericardium and contiguous structures, such as pleuro diaphragm and chest wall, it may be assumed that such adhesions were present, because the same authors reporting on the same series one year later in other publications mentioned the fact that where they failed to get "internal fibrous pericardial bands" they noted "no conspicuous changes from normal" and, hence, eliminated those dogs from their series. It seems obvious that the involvement of the epicardium in the adhesions were responsible for the hypertrophy which they observed. This, by definition, is a complication of mediastinopericarditis by adhesive pericarditis.

There are no recorded experimental observations on the relationship between uncomplicated pericardiomediastinitis and cardiac hypertrophy. The following experimental study was planned to investigate this problem.

METHOD

Ten dogs were used for this study. The first problem which presented itself was the establishment of criteria for determining hypertrophy. The criteria chosen were: (1) the weight of the heart in relation to average dog heart weights of similar size; and (2) histologic studies of biopsies of the heart taken prior to the production of the adhesions compared with histologic studies of the hearts from the same animals removed at autopsy at varying periods after production of uncomplicated mediastinopericarditis.

The animals used were mongrel dogs varying in weight from 11 to 15 kilograms. The dogs were anesthetized with intravenous Nembutal and ether. The heart was exposed by thoracotomy, the pericardium opened with minimal trauma, and a full-thickness biopsy taken from the anterior wall of the left ventricle. This was done using a cork borer, the cutting edge of which had been carefully sharpened. The diameter of this instrument was

8 mm. The wound in the myocardium was closed with fine silk. Pericardium was also closed with fine silk. This procedure was accomplished rapidly and with very little blood loss. This biopsy procedure resulted in minimal morbidity, and in dogs of this series no adhesions between the two layers of the pericardium at the site of the biopsy.

Fig. 1.

Fig. 2.

Fig. 1.—(Dog No. 5.) Biopsy of left ventricle before mediastinopericarditis.
Fig. 2.—(Dog No. 5.) Left ventricle of same dog one year after production of pericardiomediastinitis, taken at autopsy.

In order to produce the pericardiomediastinitis, talcum powder was liberally sprinkled over the closed pericardium and adjacent structures. The chest wall was then closed and the dogs returned to their cages.

RESULTS

The dogs were sacrificed at intervals varying from six months to one year. This was considered to be an adequate time to evaluate the effect of pericardiomediastinal adhesions in the myocardium.

Fig. 3.

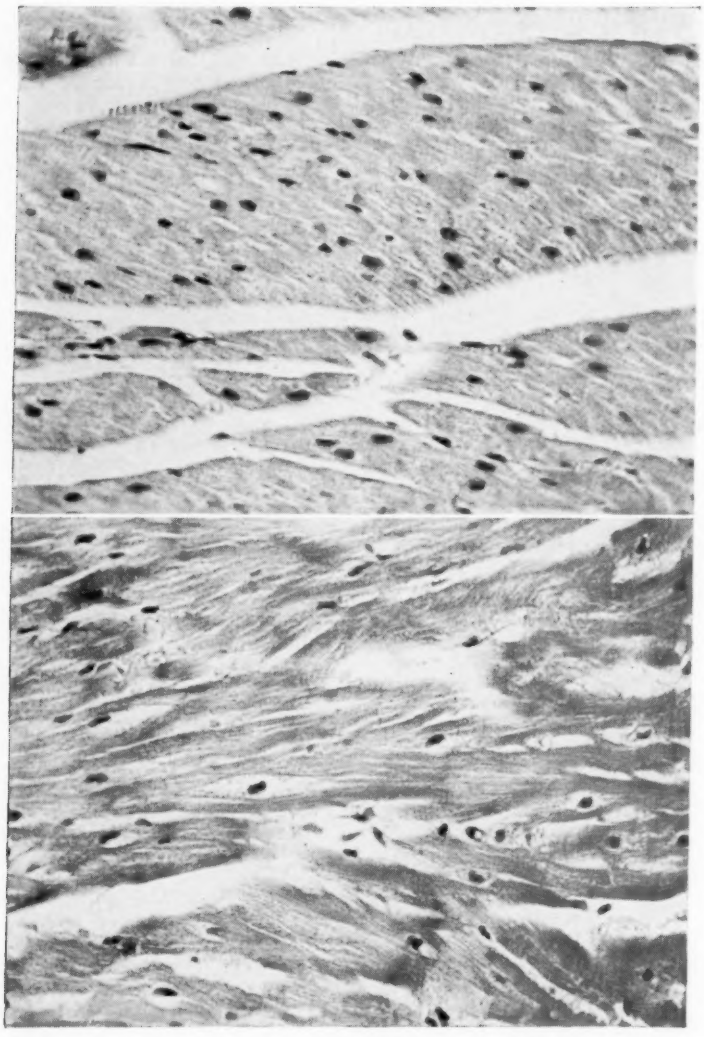

Fig. 4.

Fig. 3.—(Dog No. 8.) Biopsy of left ventricle before mediastinopericarditis.
Fig. 4.—(Dog No. 8.) Left ventricle of same dog one year after production of mediastinopericarditis, taken at autopsy.

At autopsy the heart weights were found to vary from 110 to 140 grams. Normal heart weights for dogs of this size vary from 120 to 160 grams. The heart weight of the dog is usually about 1 per cent of the total body weight.

At autopsy extensive adhesions were found in all dogs between the parietal layer of the pericardium and adjacent structures such as anterior

thoracic wall, diaphragm, and lungs. Histologic studies of the myocardium at autopsy, when compared with control sections which had been taken from the same dogs prior to the production of the pericardiomediastinitis, showed no demonstrable changes in the muscle fibers (Figs. 1 to 4). The usual histologic changes seen in cardiac hypertrophy, namely, increases in breadth of the individual fibers and the characteristic square-ended nuclei, were not present.

DISCUSSION

Neither clinical nor experimental evidence to support the contention that pure mediastinopericarditis can produce hypertrophy of the myocardium has ever been adequately produced. When hypertrophy occurs associated with pericarditis, a careful search will probably reveal a reason for it other than the pericardial adhesions. Valvular defects associated with pericarditis may result in hypertrophy. The same etiological factors which produce pericarditis may also produce endocarditis or myocarditis. The latter lesions may be responsible for the cardiac hypertrophy, particularly if associated with valvular lesions. Complications of mediastinopericarditis, such as superimposed adhesive pericarditis, may cause myocardial hypertrophy. There is no evidence that uncomplicated mediastinopericarditis can in itself produce cardiac hypertrophy.

CONCLUSIONS

In spite of occasional earlier views to the contrary, there is no evidence, either clinical or experimental, that pleuropericardiomediastinitis with adhesions and without associated adhesive pericarditis produces cardiac hypertrophy.

SUMMARY

Experimental production of uncomplicated pleuropericardiomediastinal adhesions by the introduction of talcum powder between the pericardium and adjacent structures did not result in cardiac hypertrophy in a series of ten dogs followed for a period of six months to one year.

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EXPERIMENTAL MITRAL INSUFFICIENCY

Studies of Left Atrial Pressure by Transbronchial Puncture

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THE measurement of left atrial pressure in patients with mitral valve disease by Allison[1, 2] in England, Facquet[3] in France, and Morrow[4] in this country has demonstrated the usefulness and technical simplicity of the transbronchial approach to the left atrium. In addition, Björk[5] and Kent[6] have measured left atrial pressures in several patients by paravertebral puncture of this chamber. More recently, Radner[7] has reported a suprasternal puncture technique for recording left atrial pressures. With this accumulation of clinical data, there has been renewed interest in the left atrial pressure tracings associated with various valvular lesions. In the correct interpretation of these pressure changes in different disease states may lie the key to accurate diagnosis. The purpose of this communication is to describe a method of transbronchial left atrial pressure measurement in dogs and to present data obtained in dogs with acute and chronic mitral insufficiency.

METHODS

The anatomy of the tracheobronchial tree in dogs is comparable to that in the human being and the carina and main bronchi bear similar relations to the heart and great vessels. The length of the dog's muzzle and neck and the length of the canine teeth necessitate the use of a longer bronchoscope to reach the puncture site before the handle engages the teeth. Well-documented studies in human anatomy demonstrate that an approach to the left atrium can be made with almost equal ease via either main-stem bronchus just below the carina. This is especially true of patients with enlarged left atria secondary to mitral valve disease. In the dog, however, early attempts at puncture through the right main bronchus met with little success. Bronchoscopy at autopsy with careful anatomic dissection and bronchoscopy at the time of thoracotomy with a palpating finger in the left atrium demonstrated that the most direct approach to the dog's left atrium is through the anterior inferior wall of the left main-stem bronchus, approximately 2 cm. below the carina. When the puncture is made here, the needle tip lies free in the atrium in nearly all instances. A puncture at the carina often results in artifacts in the pressure record due to the proximity of the needle point to the interatrial septum. Based on these preliminary studies the following transbronchial technique has been used.

Received for publication March 21, 1955.

Fasting dogs averaging 35 pounds are anesthetized with intravenous Nembutal (0.5 c.c. per kilogram) and secured in the supine position with their muzzles just overhanging the table edge. A gauze sponge is used to extend the tongue and elevate the mandible. This exposes the relatively long epiglottis. An extra long bronchoscope* is passed into the trachea as far as the carina. Often there is reflex coughing at this level but topical anesthesia has not been necessary. The tip of the instrument is directed into the left mainstem bronchus. At a point approximately 2 cm. beyond the carina the handle is tilted so as to impinge the open tip of the bronchoscope against the anterior inferior wall of the bronchus. As the bronchoscope is held in this position as shown in Fig. 1, the needle carrier is introduced with the other hand. With the needle held in the axis of the eventual puncture, a base-line pressure reading is obtained. Under direct vision the angulated needle is then pushed about 1 cm. through the wall of the bronchus. The needle is irrigated with saline

Fig. 1.—Dog anesthetized with tracheoscope in position. Transbronchial left artrial pressure being recorded.

solution by a syringe connected to the system via a three-way stopcock. The left atrial pressure curve is recorded and the zero reading rechecked on withdrawal of the needle into the bronchoscope. In some animals it is necessary to insert the needle several times before a satisfactory curve is obtained.

The various instruments used are illustrated in Fig. 2. The needle carrier is a steel tube 0.25 inch in diameter with a threaded tip to receive the hub of the needle. Different sized needles may be used but a 2-inch No. 20 needle has given the best recordings. The distal centimeter of the needle is bent upward

*Tracheoscope-Foregger-Emerson (7-9), New York, barrel length 16.75 inches.

at a 30 degree angle to the axis of the carrier. This angulation not only facilitates puncture and approximates the necessary depth of insertion through the wall of the bronchus, but also assures a freer placement of the tip within the atrium. The proximal end of the hollow carrier is fitted with a Luer Lok syringe. This is attached to a three-way stopcock soldered to one opening of a Statham transducer (P23A). The other opening of the transducer is sealed with a syringe cap. The output of the transducer is led into a suitable amplifier and direct recorder. The natural frequency of this system is approximately 18 cycles per second.

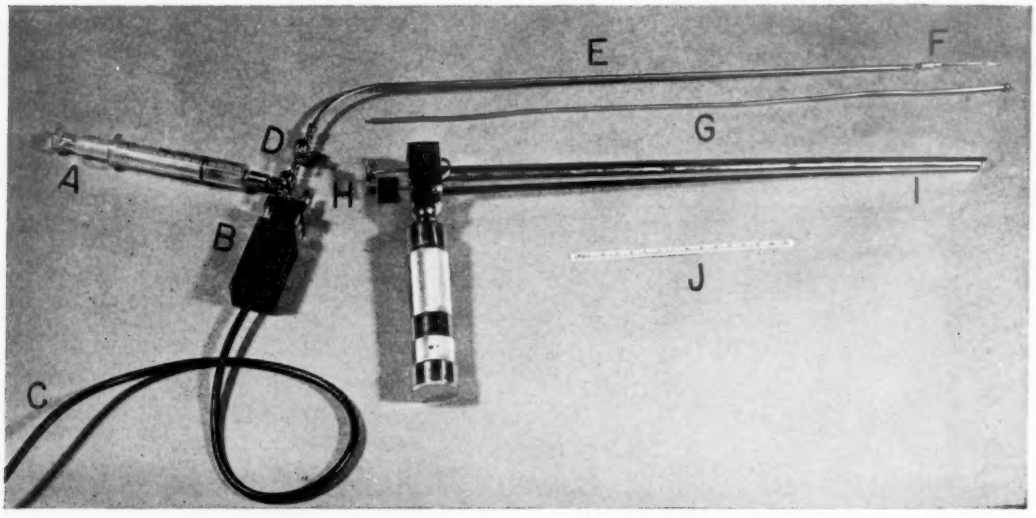

Fig. 2.—Instruments for transbronchial left atrial pressure measurement: *A*, Syringe with saline solution for flushing needle; *B*, Statham transducer; *C*, connector cable to direct recorder; *D*, three-way stopcocks; *E*, hollow steel carrier; *F*, left atrial needle with angulated tip; *G*, aspiration tip; *H*, light carrier; *I*, Foregger tracheoscope; *J*, scale in centimeters.

Using this technique, left atrial pressures were obtained in normal dogs prior to thoracotomy. These dogs were then operated upon and direct left atrial pressure measurements made using the same recording system. Mitral regurgitation was produced using both a left atrial appendage approach with cutting of valve leaflets and a left ventricular approach with severance of chordae tendineae.[8] Left atrial pressures were recorded directly through a No. 20 needle before and after regurgitation was produced. Standard electrocardiograms were recorded simultaneously.

Transbronchial left atrial pressure measurements were made in the immediate and late postoperative survival periods. The time between operation and transbronchial recording ranged between 4 and 144 days. Specific measurement was made of the atrial systolic pressure or A wave, the early atrial diastolic pressure or X wave, and the last positive pressure in late atrial diastole, the V wave.

RESULTS

Left atrial pressures were recorded transbronchially in 10 normal dogs. An example of these pressure curves is shown in Fig. 3. In normal dogs the

A- and V-wave components were equal. The A-wave pressures were between 4 and 10 mm. Hg with an average of 7.8 mm. Hg. The X-wave pressures were between −1 and 3 with an average of 1.3 mm. Hg. The calculated average left atrial mean pressure was 3.5 mm. Hg.

Left atrial pressures were recorded directly with the chest open in 16 dogs, including the 10 studied transbronchially. An example of these pressure curves compared with one obtained in the same dog transbronchially is shown in Fig. 4. The ranges in A- and X-wave pressures were similar to those obtained transbronchially. The average A-wave pressure was 7.0 mm. Hg; the average X-wave pressure was 1.8 mm. Hg. The average left atrial mean pressure was 3.5 mm. Hg, the same as that obtained transbronchially.

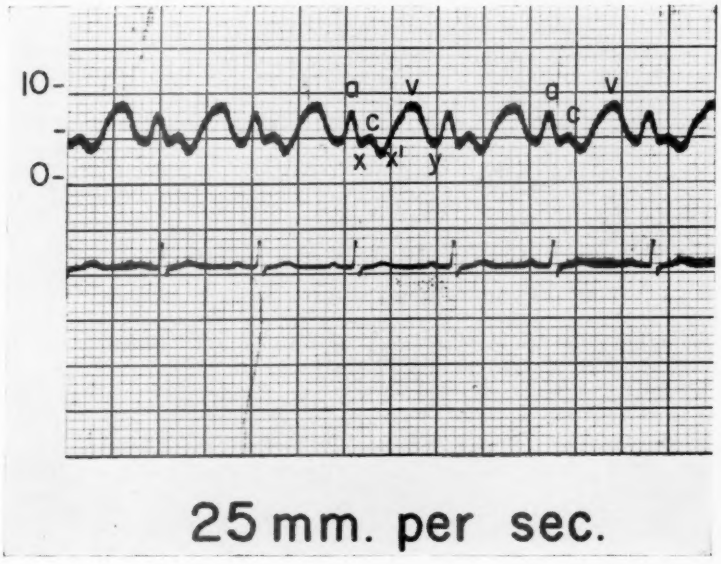

Fig. 3.—Left atrial pressure curve of normal dog recorded transbronchially. Component waves are labeled.

Mitral regurgitation was produced in 22 dogs. The valve leaflets were cut in 10 dogs via the atrial appendage; 6 of these dogs had marked regurgitation produced and 4 had minimal regurgitation.[8] In 12 dogs, regurgitation resulted from selective severance of chordae tendineae through the left ventricle; all had marked regurgitation.

Left atrial pressures were recorded directly in 18 dogs with mitral regurgitation. Sixteen of them were classed at operation as marked regurgitation. Representative left atrial curves before and after regurgitation are shown in Fig. 5. Direct measurement of pulmonary artery pressure revealed no acute postregurgitation changes. The V wave was uniformly elevated and always higher than the A wave. The range of V-wave pressures was between 9 and 35 mm. Hg. The range of X-wave pressures was between 0 and 17 mm. Hg. The average V-wave pressure was 16.6 mm. Hg and average X-wave pressure was 4.2 mm. Hg. The average left atrial mean pressure was 8.1 mm.

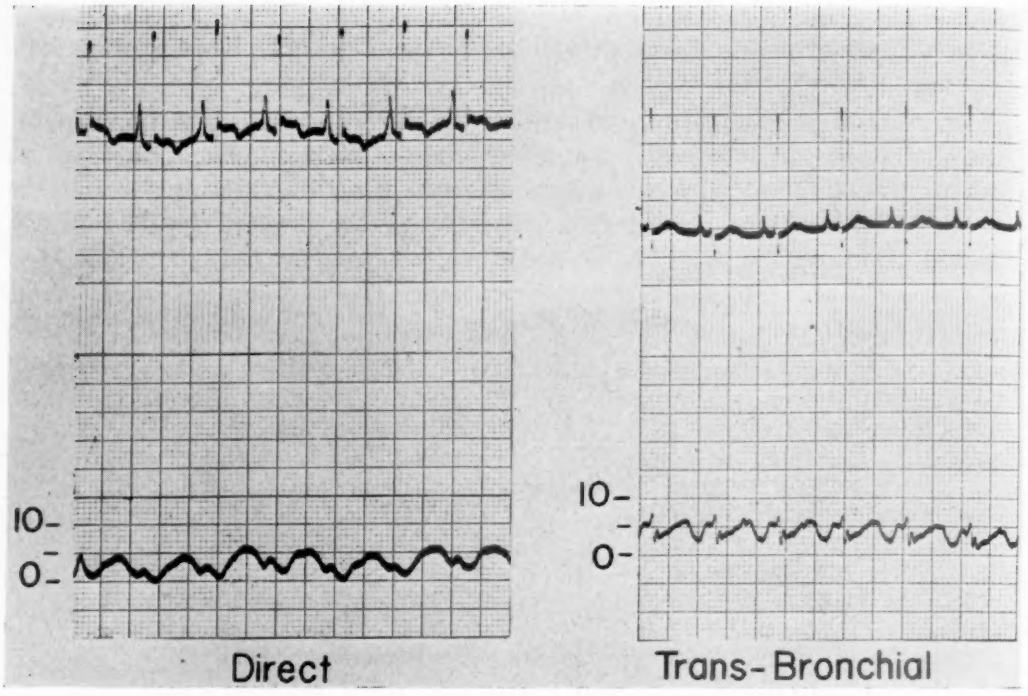

Fig. 4.—Left atrial pressure wave of normal dog recorded transbronchially and directly at operation.

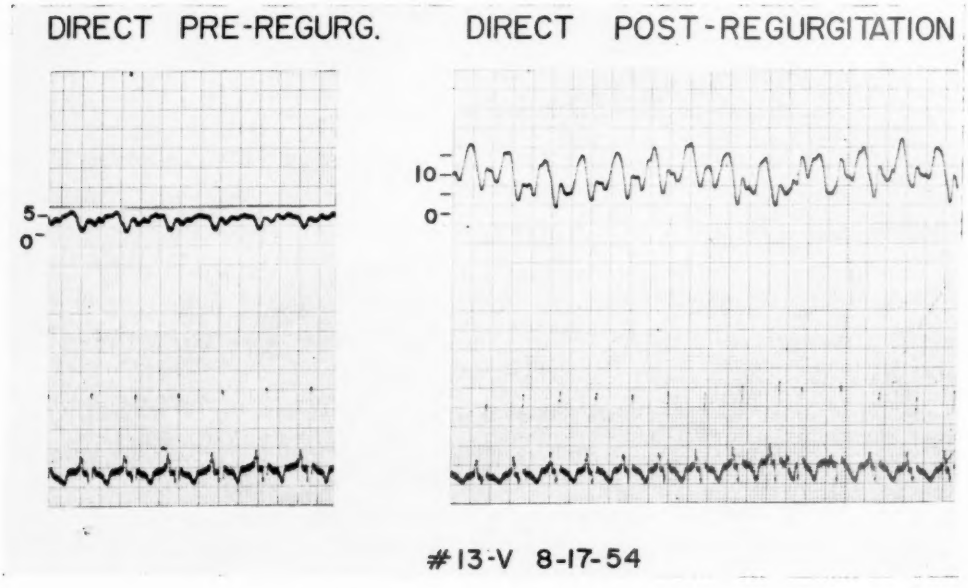

Fig 5.—Left atrial pressures at operation in Dog 13V.

Hg. In 2 dogs with minimal regurgitation, V-wave pressures were measured directly. They were 10 and 13 mm. Hg. The X-wave pressures were 0 and 3 mm. Hg. The average left atrial mean pressure was 4.8 mm. Hg.

Fifteen dogs survived longer than seven days after operation; however, illness or sudden death limited transbronchial left atrial pressure measurements to 13 dogs. In several dogs serial records were obtained. Fig. 6 shows the transbronchial left atrial pressure curve in Dog 4V before and after regurgitation. The curve forms and pressure ranges were similar to those obtained by direct measurement. In the group with marked regurgitation the average V-wave pressure was 19.2 mm. Hg and the average X-wave pressure was 8.1 mm. Hg; the average left atrial mean pressure was 11.8 mm. Hg. In the group with minimal regurgitation the average V-wave pressure was 11.5 and the X-wave pressure was 3.8; the average left atrial mean pressure was 6.4 mm. Hg.

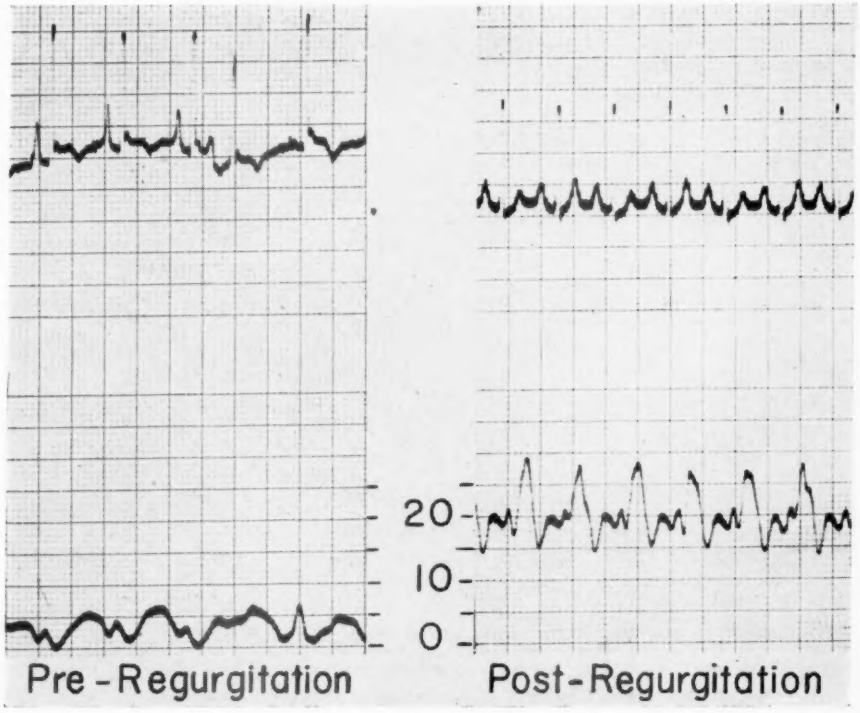

Fig. 6.—Left atrial pressure recorded transbronchially before and after regurgitation in Dog 4V.

In several dogs simultaneous left ventricular and left atrial pressure curves were obtained so that the temporal relationship between their components could be analyzed.

The results of the left atrial pressure measurements are summarized in Table I.

DISCUSSION

The components of the normal left atrial pressure curve are shown in Fig. 3.[9] The first wave of positive pressure in the left atrium is produced by

TABLE I

DOG NUMBER	LEFT ATRIAL PRESSURES (V WAVE / X WAVE) DIRECT PREREGURG.	DIRECT POSTREGURG.	TRANSBRONCHIAL POSTREGURG.	CAUSE OF DEATH
1A	7/3	35/8		Mod. acute pulm. edema (2)
2A	9/5	13/4	12/3 (47)	Sac. (47)
5A	8/1	18/8	17/8 (24) 8/3 (45) 12/2 (81)	Alive (107)
3M			18/3 (27) 12/3 (59)	Sac. (62)
7M		10/3	9/4 (36)	Sac. (103)
1-PA	5/1	12/1 9/2 (29)		Sac. (29)
2V			13/3 (4)	Sac. (18)
3V	6/2	17/4		Oper. death 2 hr.
4V	7/2	14/3	30/17 (34)	Acute pulm. edema (34)
5V	8/2	12/0		Acute pulm. edema (14)
7V	6/1	30/10		Acute pulm. edema (1)
8V	7/0	19/0, 10/0	9/4 (18)	Alive (44)
9V	7/2	26/17		Acute pulm. edema (2)
10V	8/1	9/1		Myocardial damage, acute pulm. edema (2)
11V	6/0	12/0	15/6 (7)	Alive (33)
12V	6/1	18/2	50/25 (52)	Acute pulm. edema (53)
14V	7/1	14/4		Acute pulm. edema (1)
15V	8/1	11/3		Acute pulm. edema (1)
		Av. V wave 16.6 Av. X wave 4.2 Mean 8.1	Av. V wave 19.2 Av. X wave 7.6 Mean 11.5	
	No. marked regurgitation 18			

DOG NUMBER	LEFT ATRIAL PRESSURES DIRECT PREREGURG.	DIRECT POSTREGURG.	TRANSBRONCHIAL POSTREGURG.	CAUSE OF DEATH
3A	5/1	13/3	10/5 (45) 8/3 (80)	Sac. (120)
1M			11/1 (67)	Sac. (70)
2M			15/9 (28) 12/6 (108) 5/0 (144) 9/5 (192)	Sac. (192)
6M		10/0 (68)	10/0 (28)	Sac. (68)
		Av. V wave 11.5 Av. X wave 1.5 Mean 4.8	Av. V wave 11.5 Av. X wave 3.8 Mean 6.4	
	No. minimal regurgitation 4			

( ) = days.

the contraction of the atrium and is termed the A wave. The immediate fall in atrial pressure after atrial systole produces the first negative wave, or X wave. The second positive wave follows almost immediately. It occurs during isometric ventricular contraction and is thought to be due to a ballooning upward of the closed atrioventricular cusps into the atrium; it is the C wave. It is followed by a fall in pressure, the X′ wave; this is probably due to the drawing down of the atrioventricular septum during ventricular contraction. The third and last positive wave, the V wave, occurs near the end of the cardiac cycle in late atrial diastole, at the completion of ventricular contraction, during ejection; it is probably due to blood rushing into the atrium from the pulmonary veins, although this explanation has been questioned.[10, 11] The last negative wave, or Y wave, results from opening of the

atrioventricular valve with the flow of blood into the ventricle. The normal A wave is sharp-peaked with a narrow base, while the V wave is a gentler curve with a broad base.

The most striking change in the left atrial pressure curve after regurgitation is in the V-wave component. This is illustrated in Fig. 7. This wave is uniformly elevated and always shows a sharp upslope beginning prior to the onset of ventricular ejection and reaching its zenith with the beginning of isometric relaxation. The A wave is also relatively elevated, probably reflecting the greater diastolic filling pressure of the atrium. A C wave is identifiable in some of the postregurgitation pressure records. This seems somewhat paradoxical if the explanation of the causation of the C wave is correct. It is possible, however, that the remaining competent leaflet balloons into the overfilled, practically indistensible left atrium and produces a positive pressure deflection.

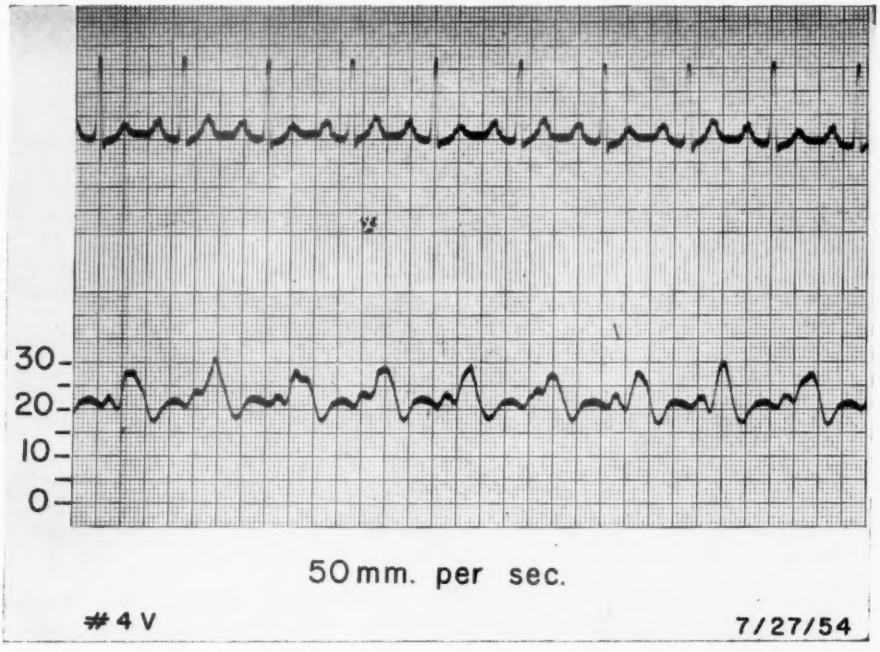

Fig. 7.—Postregurgitation left atrial pressure curve recorded transbronchially in Dog 4V.

Further analysis of the left atrial pressure curves after regurgitation reveals that the maximal elevation of the V wave occurs late in systole, near the end of the ejection phase. This is shown in Fig. 8. One might expect the reflux to be maximal by the end of isometric contraction, for then the left ventricular pressure greatly exceeds that in the left atrium. This apparent inconsistency was studied in detail by Wiggers and Feil[12] when the results of their acute experiments also indicated that the maximal reflux occurred late in systole. They felt that the briefness of the isometric contraction phase (about 0.05 second) did not allow time for the momentum of the inflowing

blood to be reversed. By the time the ejection phase began, this inertia had been overcome, and near the end of the relatively long ejection phase (about 0.2 second), the regurgitation reached its peak. This seems a plausible explanation, and one which includes the important manifestations of the dynamics of flow as well as pressure. The data obtained further support their observations that slowing of the heart rate increases regurgitation by prolonging the ventricular filling phase. More blood is therefore available for reflux with each succeeding systole. Other studies[13-19] have generally substantiated Wiggers' conclusions.

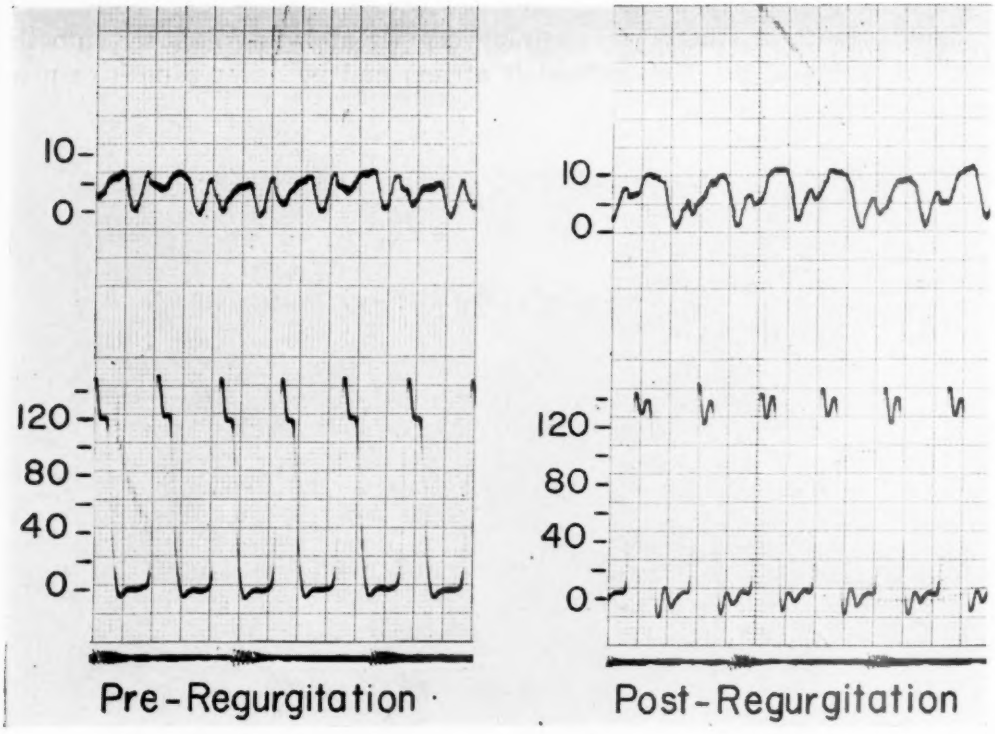

Fig. 8.—Simultaneous direct left atrial and left ventricular pressure curves before and after regurgitation.

In most cases the transbronchial left atrial pressure records were technically superior to those obtained by direct measurement because there was less artifact due to movement in the base of the heart than there was when the needle was inserted into the atrial appendage at the time of operation. The left atrial pressures recorded transbronchially were obtained with the animals deeply sedated; the pre- and postregurgitation measurements are therefore considered to be comparable. There is some question, however, whether the direct pressures measured at operation following regurgitation are strictly comparable to those obtained prior to regurgitation because of the occasional lowering of blood pressure which occurred during the operation. The left atrial pressures recorded transbronchially and directly at

operation prior to the production of regurgitation are equal as shown in Table I. This excellent correlation underlines the usefulness of the transbronchial approach.

No left atrial pressures were recorded during active physical exertion when most of the clinical symptoms of increased pulmonary pressure from mitral insufficiency become manifest. The left atrial pressures are probably considerably higher during exercise than under the conditions of measurement. This was indicated by the absence of shortness of breath and signs of pulmonary edema in the resting chronic survivors, while shortness of breath and moist râles were usually noted under the stress of severe exercise. More objective illustrations of this statement are the left atrial pressures recorded transbronchially in Dogs 12V and 4V. These animals were poorly sedated and struggled throughout the recording period. The mean left atrial pressure of Dog 12V was 30 mm. Hg; the V wave was 50 mm. Hg and the X wave 20 mm. Hg. Its immediate postregurgitation mean pressure was only 6 mm. Hg; the V wave was 13 mm. Hg and the X wave was 3 mm. Hg. Dog 4V had a similar marked increase in V-wave pressure while struggling and died in pulmonary edema. Two other animals coughed up pink, frothy sputum after prolonged exercise; one of them died of acute pulmonary edema. A satisfactory means of measuring the left atrial pressure directly, during exercise, has not been perfected.

A single example will serve to illustrate the possible use of the transbronchial method of recording left atrial pressures in studying changing lesions of the mitral valve. The left atrial pressure measured transbronchially in Dog 2M on the twenty-eighth postoperative day was 15/9 (V wave/X wave) with an elevated steep V wave considered to be diagnostic of mitral insufficiency; there was a soft apical systolic murmur. On the 108th postoperative day, the left atrial pressure was 12/6; the V wave was only questionably elevated; there was no murmur. At 144 days the left atrial pressure was 5/0 mm. Hg, and at 192 days 9/5 mm. Hg. with normal A- and V-wave components. The dog was sacrificed. The operative defect in the aortic cusp was completely healed. Four dogs with regurgitation produced by cutting the cusps alone showed hemodynamic and autopsy evidence of healing of their lesions with disappearance of regurgitation. None of the dogs with regurgitation produced by chordae tendineae severance alone showed diminution of left atrial pressures or loss of systolic murmurs.

CONCLUSIONS

Chronic mitral regurgitation in dogs produces symptoms and signs comparable to those seen in patients suffering from this valvular disease. The pressure changes occurring in the left atrium parallel those seen in patients with normal sinus rhythm and uncomplicated mitral insufficiency. What changes might result in these left atrial pressures if auricular fibrillation were superimposed has not been determined. The sharply inclined, elevated V wave appears to be the hallmark of pure mitral regurgitation.

SUMMARY

A method of transbronchial left atrial pressure measurement in dogs is presented. Studies of the left atrial pressures in normal dogs and in dogs with experimental mitral insufficiency are reported. A discussion of the pressure changes associated with chronic experimental mitral regurgitation is given and a correlation suggested between them and the left atrial pressure curves in patients with mitral insufficiency.

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INTRAVENOUS CHOLANGIOGRAPHY AND CHOLECYSTOGRAPHY

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INTRODUCTION

ALTHOUGH oral cholecystography has proved to be an accurate and satisfactory diagnostic procedure, it has well-recognized limitations. This becomes evident in those conditions in which delineation of the biliary ducts appears desirable or in which the gall bladder remains nonopaque due to its inability to concentrate the contrast medium. There are also selected cases in which a more rapid cholecystographic examination would prove to be advantageous. It is therefore readily apparent that a contrast medium which would be excreted in sufficiently high concentration by the liver to opacify the intra- and extrahepatic duct system would further expand the field of roentgen diagnosis of biliary tract disorders.

A most significant contribution to cholangiography and cholecystography was made by Jones and his associates[5] at the University of Rochester. These authors, on testing (0-4-hydroxy-3,5-diiodobenzyl)-benzoic acid, observed that this compound, both on intravenous or oral administration, would opacify the biliary ducts in experimental animals with great regularity. Subsequently, other investigators[7, 9, 10] have shown that several other cholecystographic media may also opacify the common duct or even hepatic duct system, provided that special administration techniques are employed.

Recently a new compound has been introduced by Langecker, Harwart, and Junkmann[6] which may lead to further advances in cholangiography and cholecystography. This compound on intravenous administration will be excreted by the liver in sufficient concentration to render the intra- and extrahepatic duct system radiopaque. Since this medium also readily opacifies the gall bladder, it constitutes at the same time a suitable compound for rapid cholecystography.

Initial clinical results,[1-4] largely reported in the foreign literature, appear promising, although it is apparent that the value of intravenous cholangiography will have to be determined by much more extensive clinical application in a large variety of pathologic states. At this time, however, it may be warranted to give a preliminary report of our clinical experience with intravenous cholangiography with emphasis on such observations as toxic side reactions, effect on liver function, and renal excretion of the contrast medium.

Received for publication Jan. 14, 1955.

CONTRAST MEDIUM AND METHOD OF STUDY

Cholografin is a 20 per cent colorless aqueous solution of the Disodium salt of N,N′-adipyl-bis-(3-amino-2,4,6,-triiodo)-benzoic acid.* The contrast medium has an iodine content of 64.32 per cent and is almost isotonic.[2] Since the compound is poorly absorbed by the gastrointestinal tract, it has to be administered intravenously. Under normal conditions, approximately 90 per cent of the contrast medium is excreted by the liver, the remainder being eliminated by the kidneys.[2] As, with this iodine containing contrast medium, untoward reactions of the patients may be expected, the same precautions as on intravenous urography were taken.

Most of our patients received 40 c.c. of Cholografin by slow intravenous injection, although occasionally 20 c.c. and, in one instance, 60 c.c. was administered. The patients were usually examined in the fasting state, except for those patients in whom immediate examination appeared desirable. Radiographic examinations were performed with the subjects in left anterior oblique prone position, occasionally supplemented by additional projections as well as laminography. Following intravenous injection of the contrast medium, roentgenograms of the liver and gall bladder region were obtained at 10- to 20-minute intervals for a period of one to two hours.

Intravenous cholangiography and cholecystography were performed 48 times in 46 patients. Five of these patients had disorders entirely unrelated to the biliary tract and may be considered as normal individuals. The other patients had symptoms compatible with biliary tract disease or proved hepatic, biliary tract, or pancreatic disease. There is little doubt that in this latter group individual patients with normal biliary tract functions are also included.

SIDE EFFECTS

Side reactions incident to the use of Cholografin have generally been no more severe than those accompanying the use of commonly employed agents for intravenous urography. Nausea and vomiting have been encountered most frequently. Flushing of the skin, itching, and a peculiar taste in the mouth were

TABLE 1

	INJECTION TIME FIVE MINUTES AND MORE	INJECTION TIME FIVE MINUTES OR LESS
Total number examinations	38	10
Nausea	7	5
Vomiting	2	2
Itching	1	1
None	24	5

other reactions noted by the patients. At least five minutes was taken to inject the contrast medium in 38 examinations, whereas less than five minutes was employed for ten patients. In this latter group with shorter injection time, side reactions occurred more frequently. The major side reactions observed in this study are briefly listed in Table I. All of these side effects were transitory

*This contrast medium was kindly provided by Dr. Mark H. Lund, The Squibb Institute for Medical Research.

and lasted no longer than five minutes, with the exception of those occurring in one individual. This patient, who had also received blood transfusions and penicillin, developed itching and urticaria nine hours following intravenous cholangiography.

EFFECT ON LIVER FUNCTION

Since Cholografin is primarily excreted by the liver, an attempt has been made to determine whether its clinical application would adversely affect hepatic function. The metabolic and excretory activities of the liver are numerous, and no single laboratory test provides an adequate index of pathologic changes. We have utilized in the evaluation of hepatic function the determination of Bromsulphalein retention and serum protein levels, as well as the cephalin flocculation and thymol turbidity tests.

In 42 of a total of 48 examinations, these laboratory studies were carried out shortly before and within one to seven days following intravenous cholangiography. Another series of liver function tests was repeated from 11 to 64 days following the examination with Cholografin in 17 patients to detect latent liver function changes.

No significant changes were observed in this study, with three exceptions. These changes, showing increased impairment of hepatic function, were thought to be compatible with the normal course of the disease involved. One of these patients had a progressively downhill course due to carcinoma of the kidney with extensive liver metastases. Another patient with chronic cholecystitis had a rise of the Bromsulphalein retention from 6 to 14 per cent at a time when the patient's clinical condition worsened, requiring surgical intervention. A third patient with duodenal ulcer and paraduodenal abscess formation showed a 6 per cent Bromsulphalein retention twelve days following cholangiography. There were five patients in whom this test improved or returned to normal levels following cholangiography in correlation with the clinical course of these individuals.

From these studies it appears that Cholografin, administered in doses currently recommended, will not impair liver function to a degree that is recognizable by the tests employed.

Blood urea nitrogen levels were similarly investigated in an effort to determine possible adverse effect on renal function. Minor changes occurred which in most cases could be well explained by the large variation in the clinical status of the patients.

RENAL EXCRETION

In 30 of the 48 intravenous cholangiograms, the renal excretion of the contrast medium could be observed by opacification of the calyceal system or renal pelvis. The visualization of the renal structures was most marked ten minutes following injection of the contrast medium but usually persisted for another 20 to 30 minutes. It has been suggested that observation of renal excretion may represent a sign of impaired hepatic function as, under such circumstances, the renal elimination of the contrast medium may be the preferred mode of excretion.[3]

Our studies are not in accord with this concept. Renal excretion of Cholografin was noted in 15 of 20 patients who had, according to our laboratory studies, varying degrees of impaired hepatic function. This was expected as there were patients with biliary tract obstruction in this group. Renal excretion was also observed in 12 of 23 patients with normal liver function. The visualization of contrast medium in the upper urinary tract 10 to 30 minutes following the injection of Cholografin should therefore not be considered as indicative of hepatic disease.

It is likely that quantitative determinations of iodine excretion by the kidney will give a more reliable index of the degree of liver damage.

Fig. 1.

Fig. 2.

Fig. 1.—Intravenous cholangiogram 20 minutes following injection of Cholografin. The common bile duct is well outlined. Some of the contrast medium has passed into the duodenum.

Fig. 2.—Intravenous cholangiogram 40 minutes following injection of Cholografin. The intra- and extrahepatic ducts are visualized. Beginning opacification of gall bladder. Note contrast medium in renal calyces.

CLINICAL RESULTS

Under normal conditions, faint opacification of the biliary duct system occurs ten minutes following injection of Cholografin. More intense opacification may be noted in roentgenograms taken from 20 to 40 minutes following injection of the compound (Figs. 1 to 3). Frequently the biliary duct may remain visible for a period of one to two hours.

Filling of the gall bladder with the contrast medium may commence 30 minutes after the beginning of the examination, but a satisfactory cholecystogram is usually not obtained until 60 to 120 minutes have elapsed (Fig. 4). As there is in early roentgenograms a very incomplete mixing of the contrast medium with the residual gall-bladder bile noted, spurious filling defects may occur which are easily mistaken for gallstones (Fig. 5, *a*, *b*, and *c*).

In all five patients whose clinical symptomatology was not related to the biliary tract system, very satisfactory opacification of the biliary duct and gall bladder was obtained. It is noteworthy that in these subjects the diameter of

Fig. 3.—Opacification of hepatic duct and common bile duct 40 minutes following injection of Cholografin.

Fig. 4.—Intravenous cholangiography. One-hour roentgenogram. *a*, Common hepatic duct; *b*, cystic duct; *c*, common bile duct. Gall bladder intensely opaque.

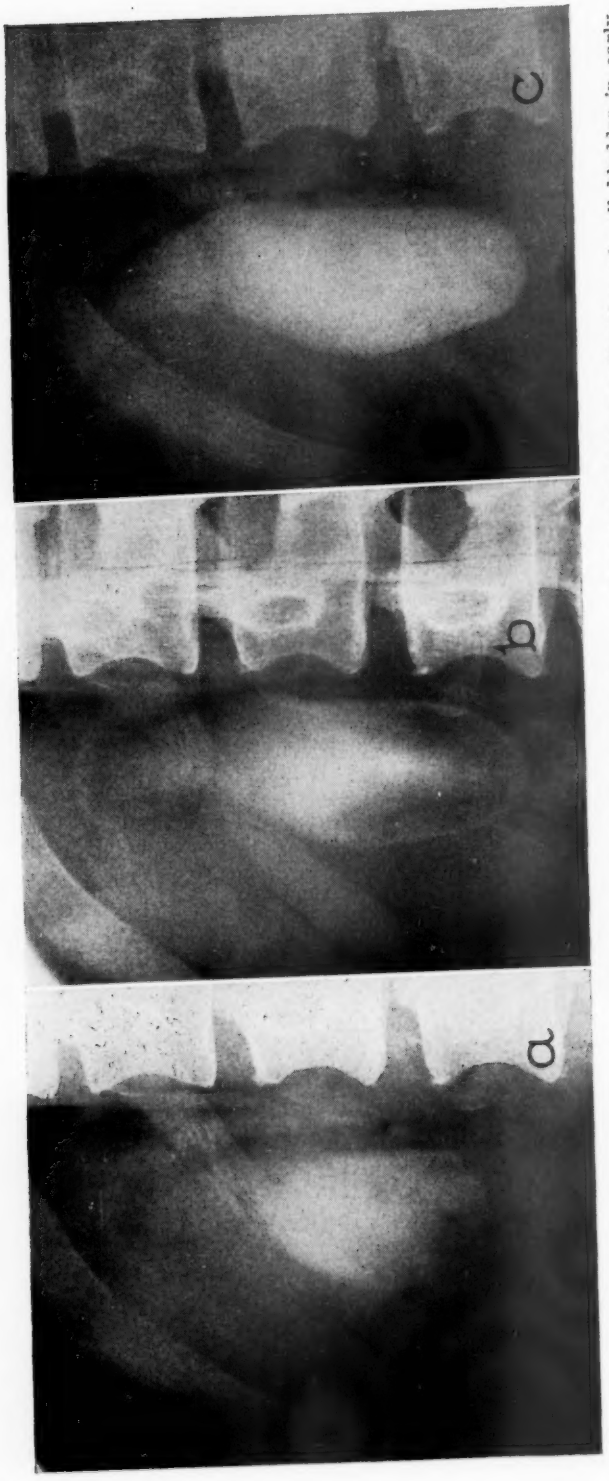

Fig. 5.—Filling of gall bladder. *a*, 40 minutes; *b*, one hour; *c*, two hours. Note incomplete opacification of gall bladder in early roentgenograms.

the common bile duct measured 2 to 4 mm., whereas, in all other patients examined in this study, variations in the diameter of this viscus from 2 to 14 mm. were encountered. There exists, as yet, no well-established standard of average and maximum diameters of the normal common bile duct. Some investigators[4] consider a diameter of 4 to 5 mm. as a maximum value, whereas others[8] regard measurements up to 8 mm. within the normal range. It is hoped that by wider application of intravenous cholangiography to normal individuals more precise information concerning the diameter may be obtained. This is a prerequisite to recognition of pathologic common duct dilatation.

In addition to the normal individuals, intravenous cholangiography was performed in 41 patients with a large variety of pathologic conditions, such as acute cholecystitis, chronic cholecystitis with and without cholelithiasis, chronic pancreatitis before and after sphincterotomy, pancreatic cyst, Laennec's cirrhosis, infectious hepatitis, and duodenal ulcer. Several patients were examined following cholecystectomy and there was a group of patients in whom a definite clinical diagnosis could not be established.

Obviously, the number of patients with this large variety of pathologic conditions is too small to permit definite conclusions. Nevertheless, in several disease entities certain impressions were gained. There was a group of 8 patients with acute cholecystitis in whom intravenous cholangiography was performed early in the course of the disease. In none of these patients was it possible to obtain opacification of the gall bladder, but, in 5 of these patients, common duct visualization was noted. In one instance, the common bile duct was found to be dilated.

The results in patients with clinical jaundice were disappointing. Visualization of the gall bladder and biliary duct system succeeded in only 1 of 9 patients. These patients had hepatic dysfunction which made satisfactory excretion of the contrast medium unsatisfactory. In 4 patients without clinical jaundice, but with elevated serum bilirubin levels, the gall bladder and common bile duct were opacified in two instances.

So far, we have not been able to demonstrate a stone in the common bile duct, although others have been able to accomplish this under favorable conditions.[3, 4] In 24 patients of our series subjected to biliary tract surgery, a common duct stone was found on operation in only one patient. In this individual, who was jaundiced, neither the biliary duct system nor gall bladder was opacified on intravenous cholangiography. Undoubtedly in the diagnosis of common duct stones, intravenous cholangiography could make a most important contribution. We believe that only by more extensive application of intravenous cholangiography to patients in whom common duct stones are suspected may the value of this method be determined.

One may speculate as to the merits of intravenous cholangiography in the evaluation of patients following sphincterotomy for chronic pancreatitis. In one of our patients, in whom intravenous cholangiography following this procedure was employed, a flooding of the duodenum with the compound was noted which may well indicate that adequate surgery had been performed (Fig. 6).

Fig. 6.

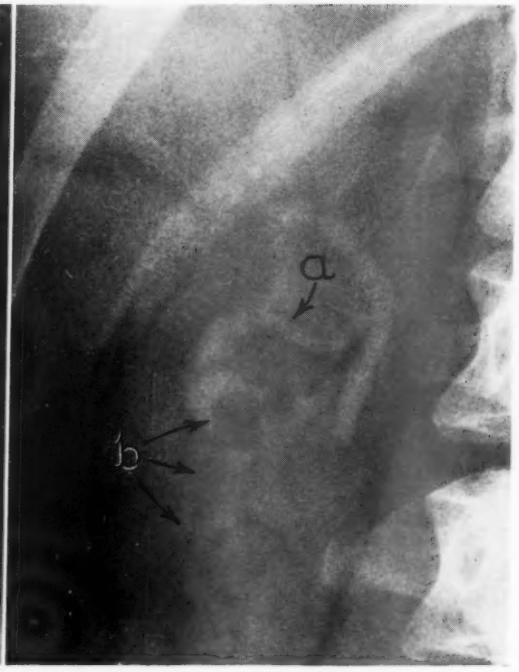

Fig. 7.

Fig. 6.—Intravenous cholangiogram postsphincterotomy for chronic pancreatitis. The 40-minute roentgenogram reveals a large amount of contrast medium in duodenum.

Fig. 7.—Demonstration of gallstones. Previous cholecystograms did not opacify gall bladder. *a*, Cystic duct; *b*, gallstones.

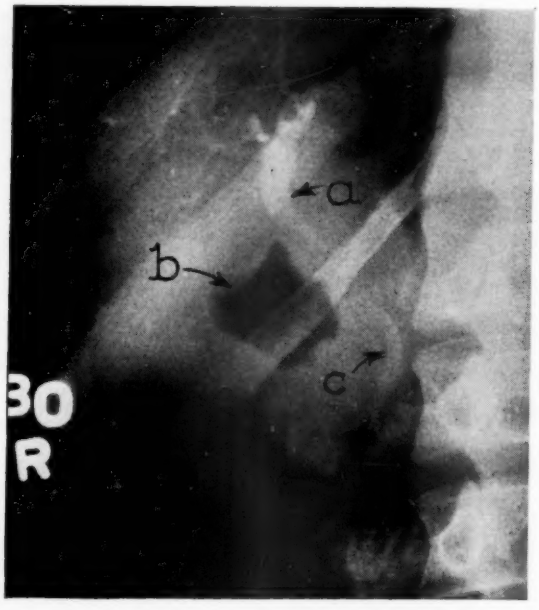

Fig. 8.—Intravenous cholangiogram in patient with duodenal ulcer and perforation. *a*, Dilated hepatic duct; *b*, perforation pocket; *c*, common bile duct. The patient had slightly elevated serum bilirubin levels.

The examinations in two other patients merit brief description. In one patient, nonopacification of the gall bladder was encountered on two occasions following oral cholecystography, even with double dose contrast medium. Following intravenous cholangiography, it was possible to visualize the cystic duct and the gall bladder, which in this instance contained several large calculi (Fig. 7). In this examination, intravenous cholangiography proved to be superior to oral cholecystography.

In another patient with duodenal ulcer and large perforation pocket, intravenous cholangiography clearly demonstrated the close interrelationship of this cavity with the biliary duct system. This patient, who had a slightly elevated serum bilirubin level, was found to have a dilated hepatic duct system, whereas the common duct had remained normal in caliber (Fig. 8).

SUMMARY AND CONCLUSIONS

1. Cholangiographic and cholecystographic studies with a new contrast medium, Cholografin, are described. This compound, following intravenous injection, is excreted by the liver in high concentration rendering the biliary duct system radiopaque within 10 to 20 minutes. Satisfactory visualization of the gall bladder, equaling in quality that obtained with oral cholecystography, occurs within one to two hours. The contrast medium lends itself well to rapid cholangiography and cholecystography.

2. Under normal conditions, Cholografin is largely excreted by the liver and to a small extent by the kidneys. In the presence of impaired hepatic function, increasing amounts of contrast medium are eliminated by the kidneys. In normal individuals, contrast visualization of kidney pelves and calyces is frequently observed and visualization of these renal structures should not be considered as an indication of impaired hepatic function.

3. Liver function tests performed on 42 patients before and following intravenous cholangiography did not reveal any impairment of hepatic function which could be attributed to the use of the contrast medium.

4. On slow intravenous injection of the contrast medium, toxic side reactions do not appear more severe than those observed on intravenous urography.

5. As the clinical studies were confined to only 46 patients with a large variety of pathologic conditions, definite conclusions are not warranted.

In several selected groups of patients, the following impressions were obtained:

A. In all normal individuals of this study, opacification of the biliary tract and gall bladder was prompt and satisfactory.

B. Eight patients with acute cholecystitis were studied during the early course of their disease. In none of these patients was it possible to opacify the gall bladder, but in five patients the biliary duct system could be partially or completely outlined.

C. A group of nine patients with clinical jaundice was studied. In only one patient was it possible to obtain opacification of the biliary duct system. This is unfortunate as under these circumstances demonstration of common duct stones may be difficult.

D. As the biliary duct system may be readily opacified following cholecystectomy, intravenous cholangiography may prove to be a valuable method in the study of the postcholecystectomy syndrome.

E. If oral cholecystography fails to render the gall bladder radiopaque, Cholografin may still produce a satisfactory cholecystogram and aid in a more precise determination of gall bladder pathology.

6. Our experience with this contrast medium is sufficiently encouraging to make a more extensive clinical evaluation in a larger variety of biliary tract disorders desirable.

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EOSINOPHIL CIRCULATING RESPONSE IN CEREBRAL TRAUMA

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CEREBRAL trauma and its influence upon the vegetative functions and physiologic milieu have been of increasing interest to the neurological surgeon. The effect of cerebral concussion upon the peripheral hemogram and diastase activity has been the subject of previous reports by us.[13, 14] The eosinophil response to stress situations such as surgery, trauma, hypoglycemia, and burns has been reported.[1, 3, 4, 6]

Recently Fischer,[15] in a series of cases, found a drop in eosinophils after injury. It appeared worth while, therefore, to study such a response in a comparable series of cases of cerebral trauma. The findings are similar and parallel the observations made by Fischer.

A series of fourteen patients who had sustained varying degrees of craniocerebral injury was studied. None had associated bodily trauma of clinical significance. The level of circulatory eosinophils was determined upon venous blood immediately following admission to the hospital. In five cases repeated determinations were made at daily intervals. A review of the medical histories of each of these patients failed to reveal any evidence of allergic or endocrine disease.

For purposes of standardization, control studies were made upon five patients hospitalized for nonrelated conditions. In none of these patients was there evidence of central nervous system disease or of endocrine imbalance.

In all studies the technique of Henneman was utilized.[8] All counts were completed within two hours after obtaining the blood specimen.

RESULTS

Eosinopenia was manifest on admission studies of twelve of the fourteen patients studied. The average initial level was 64 eosinophils per cubic millimeter of whole blood, with a range of 0 to 165 eosinophils per cubic millimeter of whole blood. In one case there was an eosinophil count above the accepted range of normal. One patient showed a normal count on the admission study.

Table I summarizes these results.

All control studies yielded counts that ranged between 200 and 250 eosinophils per cubic millimeter of whole blood.

Received for publication March 18, 1955.

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TABLE I

PATIENT NUMBER	AGE (YR.)	SEX	TYPE OF ACCIDENT	ADMISSION		DIAGNOSIS	X-RAY FINDINGS	EOSINOPHIL COUNT ON ENTRY	RESULT
				PULSE	BLOOD PRESSURE				
1	19	M	Auto accident	130	98/58	Hygroma; burr holes done on fourth hosp. day	No fracture	0	Improved
2	18	M	Auto accident	80	130/70	Hygroma; burr holes on second hosp. day	No fracture	224	Improved
3	46	M	Auto accident	92	190/80	Severe concussion	No fracture	66	Improved
4	45	M	Fell off trunk striking head	88	132/80	Mild concussion	Fracture	0	Improved
5	1	F	Auto accident	Unobt.	0/0	Severe concussion	Fracture	3	Died
6	5	M	Auto accident	104	122/70	Moderate concussion	Fracture	11	Improved
7	36	M	Hit with beer bottle	96	134/90	Depressed compound skull fracture	Fracture	165	Improved
8	18	M	Auto accident	100	148/90	Decerebrate rigidity	Not taken	0	Improved
9	40	F	Fell off a horse	80	130/76	Unconscious; epidural hematoma	Not taken	0	Died
10	15	M	Auto accident	90	130/80	Mild concussion	No fracture	22	Improved
11	16	M	Auto accident	96	180/70	Severe concussion	No fracture	44	Improved
12	24	M	Auto accident	64	140/78	Severe concussion	Fracture	374	Improved
13	49	M	Self-inflicted gun shot wound of head	104	110/80	Compound skull fracture; elev. and débrid. second hosp. day	Fracture	3	Died
14	50	M	Blast accident with head injury	104	118/72	Depressed skull fracture right temple region; elev. and débrid. third hosp. day	Fracture	0	Died

Serial determinations in five cases at intervals over the "posttraumatic" period revealed that in three surviving patients there was a return of the circulating eosinophils to normal levels or above, within ninety-six hours of injury. Two patients whose clinical course terminated in death showed a persistently low eosinophil count (Fig. 1).

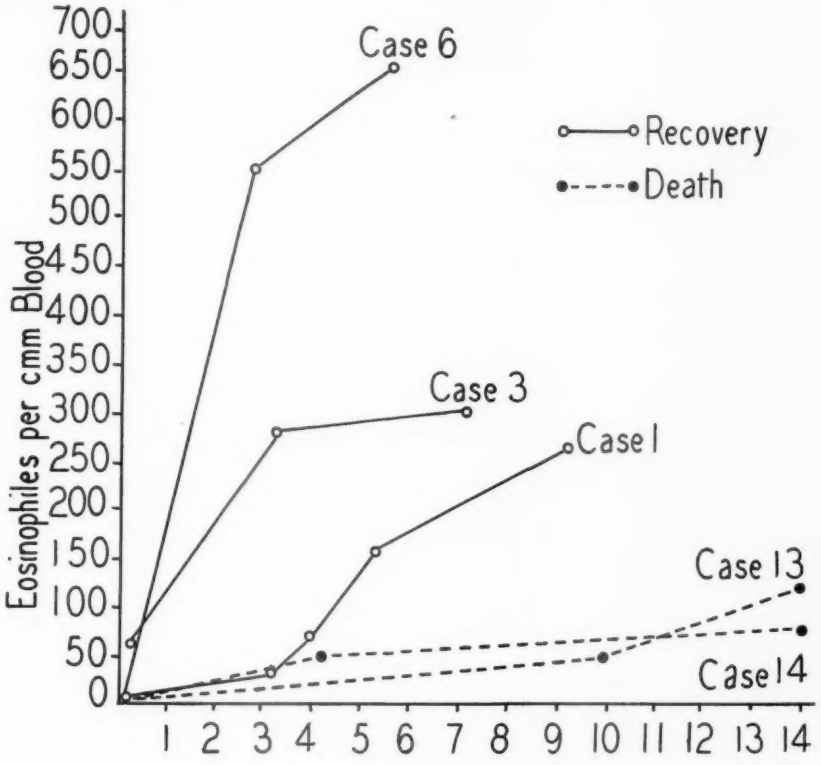

Fig. 1.

DISCUSSION

Experimental study describing the diffuse neural activity incident to cerebral concussion has been the subject of reports by Denny-Brown[2] and Gurdjian and Webster.[7] These described autonomic activity incident to cerebral injury. Hume[9] and Hume and Wittenstein[10] concluded that anterior hypothalamic stimulation resulting from systemic stress caused anterior pituitary stimulation. This increased activity was manifest by an increased liberation of adrenocorticotrophic hormone. Thorn and co-workers[15] have shown that increased concentration of ACTH results in an increased liberation of adrenal cortical oxysteroid hormones. It was observed that with an increased blood level of cortical steroids, there was a decrease in the level of circulating eosinophils. From experimental study on rats, Selye[11] concluded that increased cortin production was vital in the animal's ability to resist shock. Hence, Dalton and Selye[12] concluded that the peripheral eosinophil responses were a manifestation of the alarm reaction.

In this series of patients suffering craniocerebral trauma, there was observed a decrease in the concentration of circulating eosinophils in 85 per cent of the cases. In general, there appeared to be a correlation between the clinical improvement of the patient and the return of the eosinophil count to normal levels. In two patietns there was a persistently low eosinophil count and these subsequently died.

SUMMARY

1. This paper puts on record the incidence of eosinopenia resulting from craniocerebral trauma.

2. This study suggests a correlation between the patient's clinical course and the eosinophil count.

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EVALUATION OF ACTH AND CORTISONE IN THE TREATMENT OF BURNS

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IN SPITE of the present knowledge of the physicochemical changes that occur in burned patients and the institution of rational measures for their correction, morbidity and mortality remain high. Many patients who may be brought through the early period survive this phase only to develop severe associated complications that may prove fatal.[1]

During the initial period, attention has been directed toward preventing the immediate processes of stress. Previous investigation suggested that the use of ACTH and cortisone offered promise as a means of correcting early changes and thereby lessening late pathologic damages.[2-8] However, experience which correlated both clinical and laboratory results of controlled treatment with these substances was limited.

When burns are of minor depth and extent, the patient's response to the stress of the trauma is of less consequence and the prognosis is favorable. The somewhat more extensively burned individual may reasonably be expected to benefit from the use of ACTH and cortisone. However, if more than 75 per cent of the body surface is involved with second and third degree burns the damage is usually irreversible even though the patient survives the initial phase. The so-called borderline case, in which the outcome is questionable soon after injury, requires special consideration. Laboratory evidences of shock, such as hemoconcentration, urinary changes, and electrolyte disturbances, may be absent or not marked. Failure to appreciate the fact that clinical or laboratory evidence of the trauma is often delayed may lead to disastrous consequences during the recovery period when treatment may prove ineffective. This is particularly true of cases where 15 to 40 per cent of the body surface is involved, regardless of depth. It was this group that was thought might be benefited by the administration of ACTH and cortisone.

Initially manifested changes and the response to them may be different in any two patients, however similar their trauma. The shift of electrolytes, the hemoconcentration, and the urinary output are not always in proportion to the magnitude of the burn. Although the degree of damage to the vital organs is usually determined by the extent of the burn, minor ones may cause as extensive changes as those that involve large areas.

This study was supported by a grant from the National Institutes of Health, United States Public Health Service.

Received for publication March 18, 1955.

The immediate and late effects of the multiple damages which follow burn trauma must be considered. The immediate changes are principally related to the secondary shock and are reversible in patients with less critical burns. Those that occur during the recovery phase are more difficult to anticipate because of factors which vary with each individual. They are related both to the trauma and to its treatment. Sometimes, in spite of excellent initial treatment, late sequelae develop. However, many patients would not live long enough to develop these complications if they had not been adequately treated during the period of shock. The recovery phase, therefore, may justly be considered important. Early enthusiastic efforts at treatment must not lag, since the final results are directly related to the care demonstrated throughout the entire course.

Rationale of Cortisone Therapy for Burns.—Severe trauma places increased demands on the hypothalamus-pituitary adrenal cortical axis. It has long been known that extensive burns cause damage to the adrenal cortex, and the resultant adrenal insufficiency can be demonstrated histologically.

The regulation of the steroids secreted by the adrenal cortex is dependent on the integrity and proper function of the autonomic nervous system, the adrenal medulla, the central nervous system, pituitary gland, and the adrenal cortex. The hypothalamus, which plays a major role in the control of ACTH secretion, is influenced by peripheral stimuli and probably also by epinephrine arising from autonomic stimulation of the adrenal medulla. The stimulated hypothalamus in turn stimulates secretion of ACTH by the anterior pituitary gland. ACTH then stimulates secretion of the adrenal cortical hormones.[10] In patients with severe stress, these mechanisms must adapt to a situation which requires selective increase in the steroids necessary for survival.

An intense alarm reaction results in continued stimulation of the adrenal cortex and, if prolonged, produces adrenal cortical hyperplasia and hypertrophy. After the stimulus has been overcome, the reversible changes are restored to the original state. Through long-continued or excessive stress, the adrenal cortex can become exhausted. They may lead to severe sequelae associated with adrenal cortical insufficiency.

METHOD OF STUDY

The investigation was instituted to evaluate the effect of ACTH and cortisone on the course of severe burns. Twenty-two badly burned patients admitted to Grady Memorial Hospital were studied. They were classified as to the degree of burn and the percentage of body surface involved.[11] They were then divided into "severe" and "critical" groups according to the percentage and degree of body surface involved, age, and associated disease. Ten patients, who were classified as "severe," had burns covering less than 50 per cent of the body surface and no disabling diseases. Twelve cases were classified as "critical" on the following bases: (1) third degree burns involving 50 per cent or more of the body surface; (2) third degree burns cov-

ering 30 per cent or more of the body surface of patients past 70 years of age; and (3) third degree burns involving 35 per cent of the body surface if there were severe associated diseases or complications.

The closed method of local treatment was used on all the patients. The affected areas were superficially débrided and cleansed with normal saline

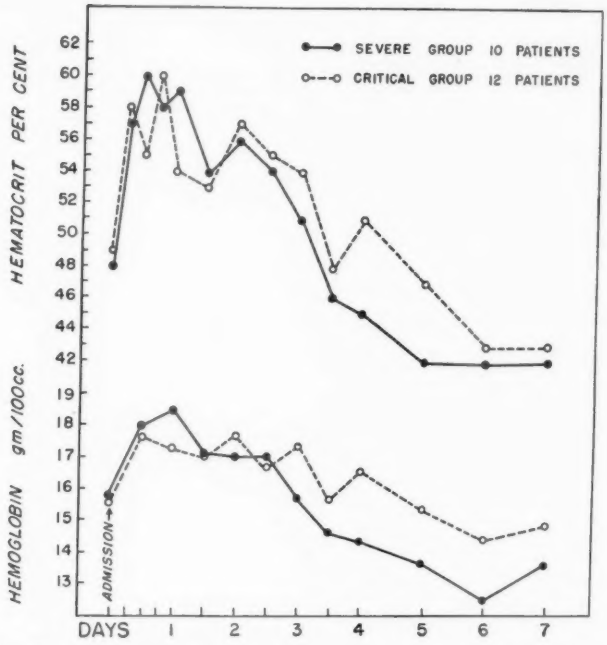

Fig. 1.—Grafts showing degree of hemoconcentration of both critical and severe groups.

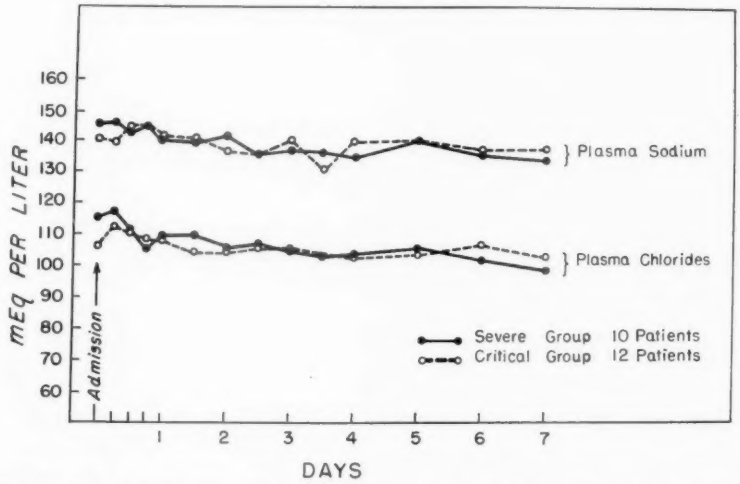

Fig. 2.—Chart showing relative plasma sodium and plasma chlorides in both critical and severe patients.

solution under sterile conditions and then covered with fine mesh petroleum jelly gauze and pressure dressings. Whenever possible, the dressings were removed in the operating room on the sixth to the tenth day. Early grafting was attempted in about three weeks.

Systemic treatment was that described by Evans and others.[12] The plan was to restore the normal balance of electrolytes, colloids, and blood as rapidly as possible. Soon after admission, the following laboratory determinations were obtained: complete blood count, hematocrit, serum sodium, chloride, potassium, blood urea nitrogen, carbon dioxide combining power, total serum protein, and total eosinophil count. In addition to the routine urinalysis, the urine sodium, chloride, potassium, and 17-ketosteroids were also determined. These laboratory procedures were performed daily for seven

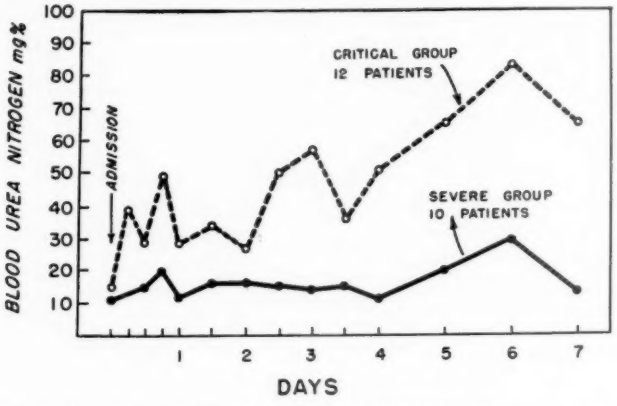

Fig. 3.—Chart showing course of blood urea nitrogen in severe and critical cases.

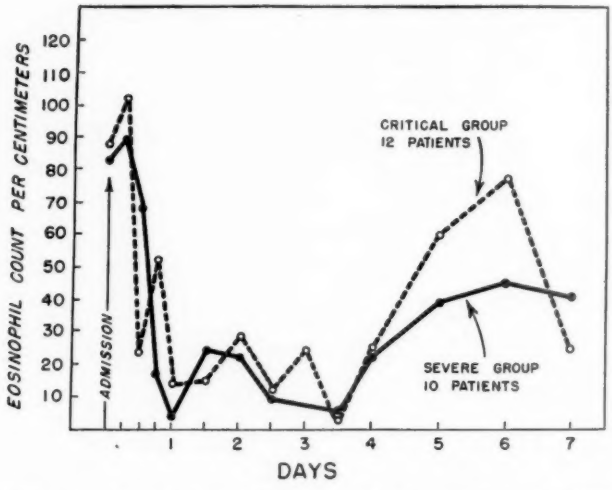

Fig. 4.—Chart showing eosinophil count in severe and critical patients.

days. The evaluation of the clinical state of the patient, degree of burn, percentage of body surface involved, and hourly urinary output provided one of the most important guides in treating these patients. An effort was made to maintain urinary output at not less than 20 c.c. and not more than 60 c.c. per hour in the adult for the first three days. Attempts were made to keep the hemoglobin below 19 Gm.

Treatment included antibiotics and, when necessary, oxygen. A Foley catheter was inserted into the bladder so that urinary output could be determined accurately. A polyethylene tube was inserted in a superficial vein for continuous administration of fluids.

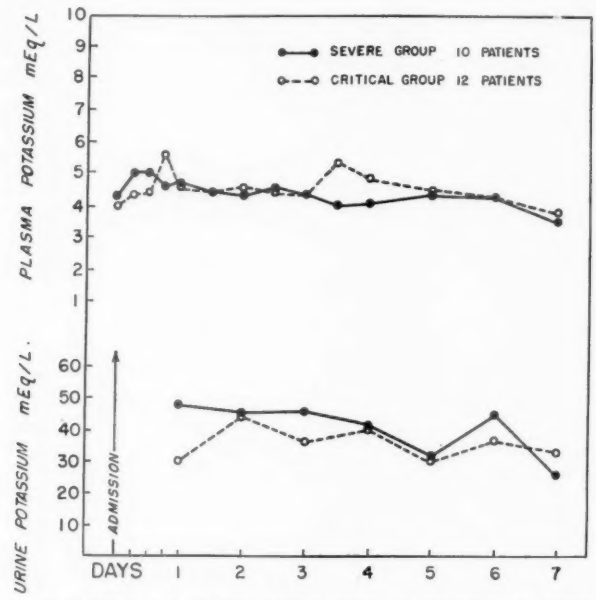

Fig. 5.—Chart showing urine potassium and plasma potassium in severe and critical patients.

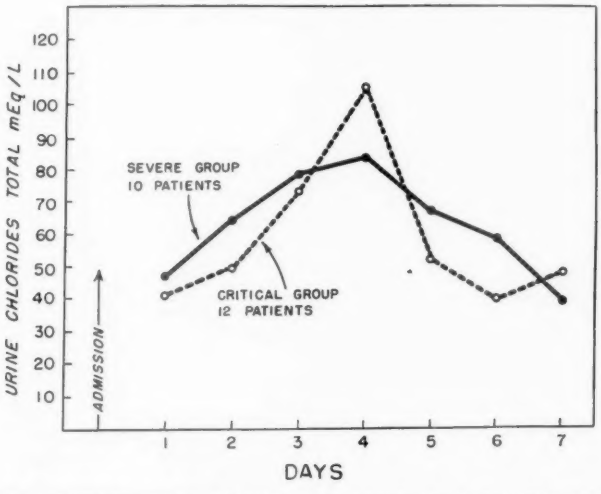

Fig. 6.—Chart showing urine chlorides in severe and critical groups of patients.

Cortisone administration was also begun at once. The adult patient was given 300 mg. the first day, 200 mg. the second day, and 100 mg. in divided doses daily for seven to eight days. If the patient was unable to take the drug by mouth, it was given intramuscularly in one-half these dosages. On the seventh hospital day, ACTH was begun, and cortisone was gradually with-

drawn. The ACTH was discontinued after three days. Some patients required additional ACTH and cortisone two to three days before and during each grafting.

The patients were carefully observed for any undesirable reactions to these substances, such as edema, hypertension, potassium deficiency and other electrolyte changes, hyperglycemia, evidences of mental deficiency, or stress ulcer.

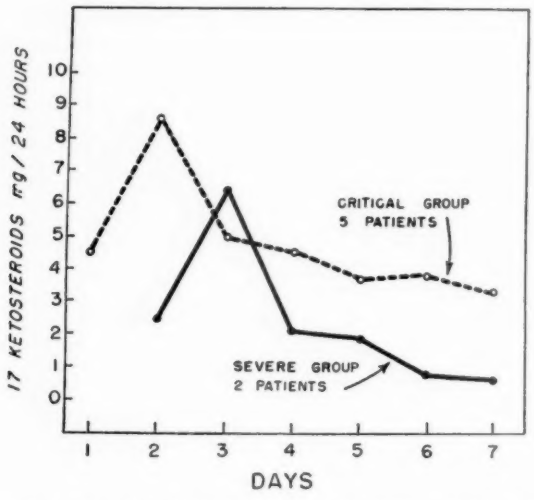

Fig. 7.—Chart showing 17-ketosteroids in severe and critical patients.

RESULTS

The patients with second and third degree burns covering 15 to 50 per cent of the body surface and with no other complications (Group 1) received the most benefit from ACTH and cortisone.

One of the most significant findings in the group was the decrease or cessation of pain within twenty-four hours after cortisone was started. There was a marked difference between the narcotic requirements of patients who received cortisone and those who did not. Of the former, only one patient with less than 50 per cent body surface involvement (Group 1) required narcotics for more than twenty-four hours after admission. Those with more extensive burns (Group 2) required, on the average, only the equivalent of one-sixth grain of morphine per day while they were on cortisone therapy. Changing of dressings caused less discomfort to patients who were given cortisone. The patients in Group 1 were generally able to sleep without sedation.

Some patients on cortisone frequently developed euphoria. One patient, whose burns covered 75 per cent of the body surface, had a sense of well-being until a few hours before death.

Anorexia, nausea, and vomiting were remarkably infrequent in Group 1 patients. All except one, who had a cerebral thrombosis a few days before

being burned, were able to take oral feedings after twenty-four hours. Within forty-eight to seventy-two hours after admission, their appetites increased and in some instances were noted to be good. The critically burned patient who was described as euphoric maintained a good appetite from the first day until shortly before death.

Good appetite was an aid in maintaining normal proteins. The stress, brought about by the severe burns, and also the effect of the administration of cortisone were counteracted by the maintenance of a good protein, fat, and carbohydrate intake which prevented a negative nitrogen balance.

An increase in the rate of epithelization, which decreased the loss of body fluid and proteins, was noted in Group 1 patients. This mechanism is thought by Seifter[13] to become activated when cortisone decreases the cellular permeability by lessening the action of hyaluronidase.

The temperature responses of patients while they were on cortisone therapy were significant. In Group 1 the average temperature during the first week was 100° F. to 101° F. During the week following cessation of the cortisone therapy, the average temperature was 101° F. to 103° F. An increase in temperature to 103° F. to 105° F. a few hours before death was characteristic of those patients who died while taking cortisone.

The patients were at all times under careful observation for evidence of inflammatory reactions, and the use of the wide spectrum antibiotics was considered essential in their prevention. In Group 1, four patients developed secondary infection of their burns while on cortisone. A 40-year-old chronic alcoholic, with a 43 per cent body surface involvement and with associated respiratory edema, required a tracheotomy. Pneumonitis developed, but the patient responded to antibiotics and bronchoscopy. A 4-year-old girl with a 35 per cent body surface burn developed pneumonia and lower nephron nephrosis and died on the sixth day while on cortisone treatment.

In Group 2, comprising the critical cases, four patients developed severe secondary infection and two developed pneumonitis while on cortisone. It was noted that those who developed secondary infections failed to show a remarkable increase in temperature.

The cortisone-treated patients who survived maintained blood pressures above shock levels with adequate blood volumes, colloids, and fluids throughout the entire period.

The incidence of so-called toxic manifestations usually found after burns either decreased or did not develop. This was evidenced by the lowered temperatures and the lack of delirium.

Allergic manifestations arising from blood transfusions and drugs were rare in these patients. One developed urticaria from penicillin a few days after cessation of cortisone.

There were three deaths in Group 1; one was due to severe gastrointestinal hemorrhages and the other two to lower nephron nephrosis. The gastrointestinal bleeding occurred in a 9-year-old girl with a 40 per cent body surface burn, and was probably secondary to a Curling's ulcer. Death from

hemorrhage occurred on the fourth hospital day. Of the two fatalities from lower nephron nephrosis, one involved a 34-year-old man with a 43 per cent burn. This patient developed sodium and potassium retention, water intoxication, secondary infection of the burned area, and adrenal insufficiency.

The mortality was 100 per cent in the twelve critical cases comprising Group 2. Six patients developed lower nephron nephrosis; three, pulmonary edema; and two, pneumonia. The twelfth, a 33-year-old woman whose burns covered 60 per cent of the body surface, developed a pulmonary infarction on the second day after her injury. It probably arose from a thrombus in the common iliac vein following insertion of a polyethylene tube for intravenous medication. The pulmonary infarction was followed by lower nephron nephrosis.

All the survivors were followed after healing. Contractures of joints involved by the burn, however, were less common than usual because the reduction in pain with the administration of cortisone had enabled the patients to exercise during the acute period.

LABORATORY FINDINGS

The hemoconcentration of the severely burned patients initially varied from moderate to pronounced, but generally responded to therapy. It was quite marked in the critical cases at first and, although it was usually quickly corrected, in one-third of the cases the hematocrit and hemoglobin remained uncontrollably high. In both groups the elevation noted within six hours of admission reached its maximum in twenty-four hours. The hemoglobin attained its maximum value of 18 Gm. per 100 c.c. of whole blood within twelve hours. Anemia was rarely demonstrable during the first seven days of therapy. Apparently, administration of ACTH and cortisone did not alter the usual course of the hemoconcentration following burns.

The plasma sodium levels were normal or slightly elevated in both groups throughout the entire period of observation. The patients who developed lower nephron nephrosis showed the customary secondary sodium retention in spite of ACTH and cortisone. No significant change in potassium levels was found except for decrease in one patient who developed congestive heart failure. The plasma chlorides, which were slightly elevated on admission, responded to therapy. In the critical group, the carbon dioxide combining power of the plasma was found to be low on admission.

As was expected, the total eosinophil count was low in both groups. Generally, it responded within eighty-four hours and continued to rise gradually. Two patients in each group, however, experienced a delayed fall in total eosinophils within seventy-two hours after admission. All four of these patients died.

During the period of observation the plasma protein levels were maintained within normal range, later dropping to 1.5 to 2.0 Gm. In three instances a mild elevation was associated with lower nephron nephrosis.

The blood urea nitrogen component was normal in all patients during the first few days. Elevation occurred only in those who developed lower nephron nephrosis, usually within five to eight days after injury.

Sugar and albumin were not usually found in significant amounts in the urine of any of the patients, although a transient glycosuria was occasionally seen. Albuminuria was quite marked when lower nephron nephrosis developed.

In the critical cases, excretion of urinary 17-ketosteroids was abnormally low, ranging between 2.5 and 4.5 for the first twenty-four hours. This was followed first by a slight rise and later by a fall to 1 to 3 mg. per twenty-four hours.

These findings indicate that administration of cortisone and ACTH permits the electrolyte fluid balance to be maintained without too much difficulty.

SUMMARY

Previous investigations suggested that patients might be benefited by administration of ACTH and cortisone during the period of stress following burns. To determine the effect of these substances, they were administered to twenty-two seriously burned patients during the first week following injury. Routine local and systemic measures were also used. Clinical and laboratory findings were carefully correlated and studied.

According to defined criteria the patients were divided into two groups, "severe" and "critical." In both groups the mortality was high, and it was felt that ACTH and cortisone had little effect on the mortality rate.

Improvement was noted in other clinical aspects, however. The patients were more comfortable during the initial period of treatment. Electrolytes, colloids, and fluids were easily controlled. The initial hemoconcentration was corrected without difficulty. None of the patients showed evidence of anemia during the first week, although it became a problem later.

Only those patients who developed severe lower nephron nephrosis experienced sodium retention. A delayed fall in the total eosinophil count was interpreted as unfavorable, since all the patients in whom this occurred failed to survive.

No serious objections were found to the use of ACTH and cortisone in burned patients.

Although the mortality rate among these patients was not decreased, it is believed that borderline patients may be carried through the initial period of stress with the addition of ACTH and cortisone to the routine treatment. On the basis of these observations, the routine use of ACTH and cortisone in the treatment of burns is not indicated.

We wish to express our appreciation to Dr. Ira Ferguson for the privilege of conducting these studies at Grady Memorial Hospital and to acknowledge the valuable technical assistance of Miss Carolyn Martin.

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CERVICAL ESOPHAGOJEJUNOSTOMY FOR EXTENSIVE STRICTURES OF THE ESOPHAGUS

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RECONSTRUCTION of alimentary continuity for extensive benign strictures of the esophagus has engaged the attention of many. Except for Yudin,[1, 2] who reported the astonishing number of 200 caustic strictures of the esophagus, 80 of which were treated surgically, there have been few reports of sizable series, as such cases are not common even in the larger thoracic clinics. This communication is a report of nine extensive benign strictures of the esophagus treated during the past four years by the method of Robertson and Sarjeant.[3] It is our hope to bring to the attention of others this quite satisfactory procedure for treatment of these difficult cases.

All are agreed that a gastrostomy life is far worse than a colostomy existence, and the ingenious methods and operations proposed and used to restore pharyngogastric or intestinal continuity attests to the efforts that have been expended.[4-6] For anyone interested in the historical aspects of medicine, the development of present-day methods over the past half century is a fascinating study. Yudin[1] and Rienhoff[7] have both given the highlights of this.

Intrathoracic esophagogastrostomy has become the standard procedure for restoring alimentary continuity following resection of the esophagus for either benign or malignant lesions below the aortic arch.[8-12] It has proved to be quite acceptable for malignant lesions and also for those due to benign strictures in the lower half of the esophagus, unless the stricture is due to esophagitis. In this instance, some other procedure is probably more satisfactory, such as esophagojejunostomy, as advocated by Allison and Johnstone.[13] However, it is the more extensive lesion which involves either all of the thoracic esophagus or at least the upper part with which we are primarily concerned in this report. What are the methods available when the anastomosis must be made either very high in the thorax or in the cervical region? In most patients the stomach can be brought up to the neck, although with an appreciable mortality rate.[12, 14-16] But, occasionally, when the esophageal stricture is due to ingestion of some strong alkali or acid, the stomach is seriously burned and becomes so reduced in size that it is no longer of use for such purposes and, in fact, may be so small as to make performance of a gastrostomy difficult. In a few instances, as in two of our nine patients, the accident had occurred in early childhood, and the disproportionate size of the stomach at that time renders high intrathoracic esophagogastrostomy less acceptable than in adults.

Received for publication Jan. 11, 1955.

The colon, either the transverse portion or the ascending colon, with or without an attached segment of jejunum, is available for transplantation.[17] It does not have such a sharply limiting vascular supply with redundant bowel as is found in the mobilized jejunum. The bacterial flora of the colon is less desirable than that of the jejunum, but with the present antibiotics this is not of great importance. There are not enough published reports of colonic transplantation with gastrocolostomy to determine with certainty the effect of gastric secretions on the colon, but, theoretically, it is less acceptable than jejunum for this reason. We have had no personal experience with the use of the colon for esophageal substitution.

Formation of an antethoracic skin tube and subsequent anastomosis to the cervical esophagostomy and to the stomach has been performed in a good number of instances, but the prolonged hospitalization required and the large number of staged operations are a powerful deterrent to this plan. It can be done and, when successful, apparently does function adequately as a food-carrying mechanism. Although hailed as a striking advance, the Torek antethoracic esophageal substitution has such serious drawbacks that most efforts of the past ten years have been directed toward development of a substitute for this very prolonged, difficult surgical feat.[1, 18, 19] However, some authors, such as von Novak,[20] are still proposing this type of esophageal reconstruction.

The other organ available for esophageal substitution is the jejunum and this has been used extensively, perhaps as often as the stomach. There are several ways in which the jejunum can be brought up for a high esophagojejunostomy. Most frequently, it has been placed in a subcutaneous tunnel over the anterior chest wall. This tunnel can be prepared blindly after the method of Yudin[1] or by a long incision with undermining of the skin edges and subsequent closure as used by Longmire.[18, 19] The two drawbacks to this method are the additional length of jejunum needed to bring it up over the costal arch and the poor cosmetic result of a subcutaneous transplantation. Yudin[1] has frequently combined a jejunal transplant with a final bridge of skin tube to lessen the length of jejunum that need be mobilized.

About ten years ago, Longmire and Ravitch[18] showed that it was possible with staged operations to transplant the jejunum into a skin tube and finally divide the mesenteric vessels so that the intestinal graft was wholly dependent upon the skin tube for vascularization. This tube could then be used as an antethoracic esophagus. They reported its use in three instances, in one of which it was completed. This ingenious plan has some merit compared with a plain skin tube antethoracic esophagus, while it has about as many or more unfavorable features.

The jejunum may also be brought up to the cervical region by passing it transthoracically through either the right or the left hemithorax.[21] Rienhoff[7] was one of the early proponents of this plan. The method employs the Roux principle of mobilizing a segment of the jejunum, but he used an antiperistaltic segment which others have not found satisfactory.

A very marked advance was that of Robertson and Sarjeant[3] which demonstrated that a passageway could be formed substernally, but extrapleurally, thus shortening the operating time and avoiding an open thoracotomy. Another advantage is that it can be performed in one stage, which is in marked contrast to the skin tube or skin tube and jejunum methods. However, the operation is flexible, also, in that it may be divided into stages and the cervical esophagojejunostomy performed at a later time if there is any question of the viability of the cervical end of the jejunum.[22] In three instances we have followed this latter plan and completed the actual anastomosis after a delay of a few days or weeks. Yudin,[1] in his extensive experience, apparently in only one or two instances used a one-stage procedure when bringing the jejunum up through an antethoracic tunnel. The Robertson-Sarjeant operation, in common with some other plans, permits two teams to work simultaneously and thus reduce the operative time.

For lesions of the lower half of the esophagus, esophagogastrostomy is so satisfactory that there is little reason to substitute an always somewhat precarious jejunal segment. It is for supra-aortic anastomoses and especially when cervical anastomosis is necessary that this type of esophagojejunostomy is most useful. Likewise, it can be employed as a sidetracking operation around an unresectable tumor of the esophagus when use of the stomach is difficult or impossible. Our first three cases were of this type,[23] but the cases here reported were all extensive benign lesions necessitating cervical or very high thoracic anastomoses. In each instance, the esophagus was divided and the distal end closed and allowed to retract into the mediastinum. There have been no complications from this distal esophageal segment.

Table I presents in summary form the benign strictures we have treated by the Robertson-Sarjeant technique, including one right transthoracic transplantation. The preoperative and postoperative roentgenograms of three of the cases are reproduced in Figs. 1, 2, and 3. There have been no deaths in this consecutive series of nine cases, but we have lost one jejunal segment.

DISCUSSION

The Robertson-Sarjeant approach has several advantages over intrapleural or antethoracic transplantation, such as the shorter distance and, thus, slightly shorter segments of jejunum that need be prepared. The substernal extrapleural route saves considerable operative time as well as avoiding an accompanying open thoracotomy. The possibility of using two operative teams is a distinct advantage but is also possible in other types of operative correction. The main disadvantage common to all methods using as long a segment of jejunum as is necessary for cervical esophagojejunostomy is the proper mobilization and yet preservation of the blood supply. The difficulty we had in the one case in which the segment was lost illustrates only too well what may happen (Case 5). The opening of one or the other pleural cavities when preparing the substernal passage is not in itself of great consequence, but there is the real possibility of the jejunum prolapsing into the pleural space and becoming kinked and obstructed (Case 5).

TABLE I. CERVICAL

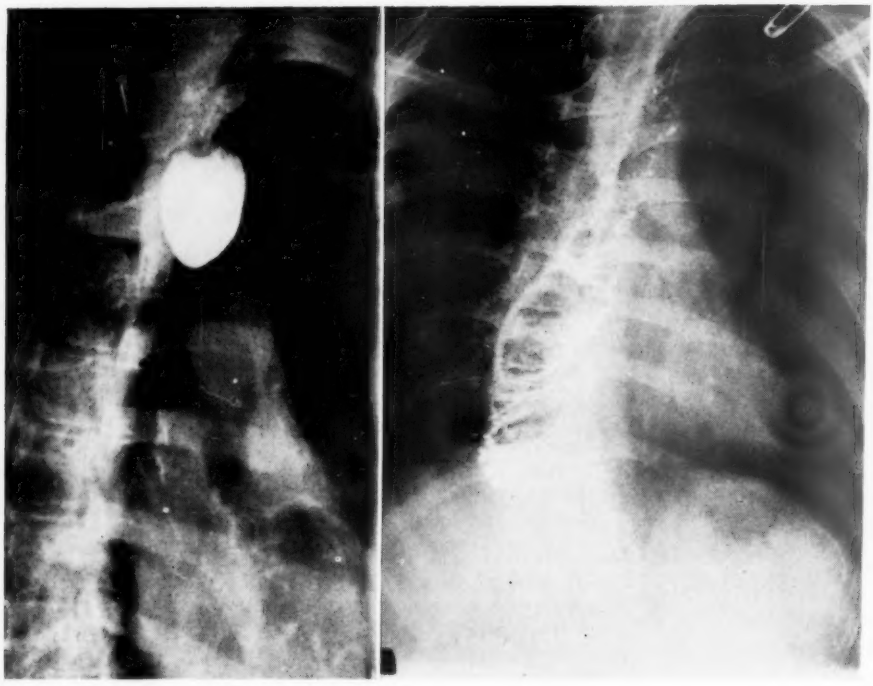
SERIAL NUMBER	HOSPITAL NUMBER	NAME	AGE	SEX	ADMISSION DATE	INJURY DATE	CORROSIVE AGENT	DILATATION ATTEMPTED PREOPERATIVELY	GASTROSTOMY PRIOR TO ADMISSION	ONE- OR TWO-STAGE OPERATION
1.	112199	J. A.	3	M	July 11, 1951	Mar. 7, 1951	Sulphuric acid	Yes	No	One
2.	115361	P. K.	17	M	Oct. 26, 1951	June 15, 1951	Sulphuric acid	No	No	One
3.	120116	F. S.	30	M	April 12, 1952	Apr. 4, 1952	Nitric acid	No	No	One
4.	121118	S.	24	M	May 15, 1952	Jan., 1952	Nitric acid	No	No, but performed preoperatively	Two
5.	124341	N. K.	20	M	Sept. 6, 1952	Aug. 17, 1952	Caustic soda	Yes	Yes	One
6.*	129951	N.	26	M	April 10, 1953	Dec., 1951	Nitric acid	Yes	Yes	Two
7.	129183	S.	2½	M	March 10, 1953	Oct., 1952	Caustic soda	Yes	No, but performed March 24, 1953	Two
8.†	7077	V. K. R.	21	M	March 23, 1954	Jan. 25, 1954	Nitric acid	Yes	No, but performed April 6, 1954	One
9.‡	22472	K.	24	M	July 24, 1954	? June 1, 1954	Nitric acid	No	No, but performed July 28, 1954	One

*See Fig. 1.
†See Fig. 2.
‡See Fig. 3.

ESOPHAGOJEJUNOSTOMY

DATE FIRST OPERATION	DATE SECOND OPERATION	ESOPHAGOJEJUNOSTOMY END-TO-END OR END-TO-SIDE	COMPLICATIONS	DISCHARGE DATE	REMARKS
July 9, 1951	-	End-to-end	Intestinal obstruction 4th postoperative day. Relieved at laparotomy	Aug. 9, 1951	This case previously reported[23]
Nov. 6, 1951	-	End-to-end	Temporary anastomotic leak	Feb. 8, 1952	Letter 3 mo. after operation stated patient feeling well, taking full diet
May 12, 1952	-	End-to-end	None	June 10, 1952	Lesion primarily lower esophagus. Esophagogastrostomy attempted on April 29, 1952, but terminated when stomach found too badly scarred and shrunken. Follow-up Feb. 24, 1953—taking full diet
June 21, 1952	Aug. 28, 1952	End of jejunum to side of pharynx	Temporary anastomotic leak	Nov. 4, 1952	Case previously reported.[22] Returned Sept., 1954, with difficulty in swallowing. Dilated on four occasions to 32F
Sept. 23, 1952	-	End-to-end	Loss of jejunal segment due to volvulous. Empyema	Transferred to plastic service June 24, 1954, for skin tube antethoracic esophagus	Probably should have attempted to bring up another segment of jejunum as antethoracic esophagus still not completed (Jan., 1955)
May 28, 1953	June 25, 1953	End-to-end	Infective hepatitis	Sept. 1, 1953	—
Oct. 23, 1953	Nov. 18, 1953	End-to-end	Developed obstruction at cervical anastomosis. On Dec. 24, 1953, anastomosis incised longitudinally and closed transversely.	Feb. 25, 1954	—
July 31, 1954	-	End-to-side	Temporary anastomotic leak	Oct. 16, 1954	Patient had marked pectus excavatum and therefore right transthoracic rather than substernal route used
Sept. 11, 1954	-	End-to-side	None	Oct. 29, 1954	

There are several points of technical importance, most of which have been emphasized by Robertson and Sarjeant.[3] Careful mobilization is of utmost necessity. Injection of procaine or similar solution around the root of the mesentery aids in peeling off the peritoneum, lymphatics, nerves, and so forth, which should be done before any vessels are ligated. In our first case, we left the first branch of the mesenteric artery and 6 or 8 inches of the jejunum



A. *B.*

Fig. 1.—Case 6. *A*, Esophagogram of Mr. N., April 11, 1953, four months after swallowing nitric acid. Esophageal dilatations were unsuccessful and a gastrostomy was performed before admission. Note the practically complete occlusion of the esophagus at the level of the clavicles. He was unable to swallow even his saliva. A first stage repair was carried out on May 28, at which time a segment of jejunum was mobilized and brought up through the anterior mediastinum after the method of Robertson and Sarjeant. The cervical esophagojejunostomy was completed on June 25. *B*, Demonstrates the result on July 8. *C*, Spot films to show the region of the anastomosis in the neck.

beyond the ligament of Treitz, but we believe that it was a mistake which necessitated the second operation. We have since that time usually taken the first artery and then divided the jejunum as high as compatible with easy jejunojejunostomy to restore continuity. Rienhoff[7] stated that the first arterial branch is always large and should be preserved in preparing the segment, which may be necessary if the antiperistaltic method is used. We have not found the arteries to decrease in size from above downward as reported by him, but rather they have varied considerably in point of origin and were frequently of varying size so that in some instances five or six small branches needed to be taken, whereas in others only three or four larger ones resulted in the same amount of mobilization.

After the jejunum has been placed in the mediastinum, it is worth while to draw back gently into the abdomen as much redundant intestine as possible before fixing it to the peritoneum. This reduces the possibility of a volvulus developing as the length of the intestine is always far greater than the length of the vascular supply. Likewise, in doing the esophagojejunostomy in the neck we have in our more recent cases performed an anastomosis between the end of the esophagus and the side of the jejunum, as in this fashion the loop of jejunum can be brought up into the neck farther than the vascular arcade.

It cannot be overemphasized that the mobilized jejunum must be handled with extreme care when transplanting it into the thorax in order that no tension be placed on the delicate vascular arcade, which is the limiting factor. In bringing the segment up through the substernal passageway, we endeavor actually to lift and push the segment rather than pull it from above. The heavy suture on the end of the jejunum is used simply as a guide and not as a means of pulling the jejunum up to the neck. For those cases where there is any question of the viability of the end of the jejunum before the anastomosis is carried out, it is wise to divide the operation into two stages as was done

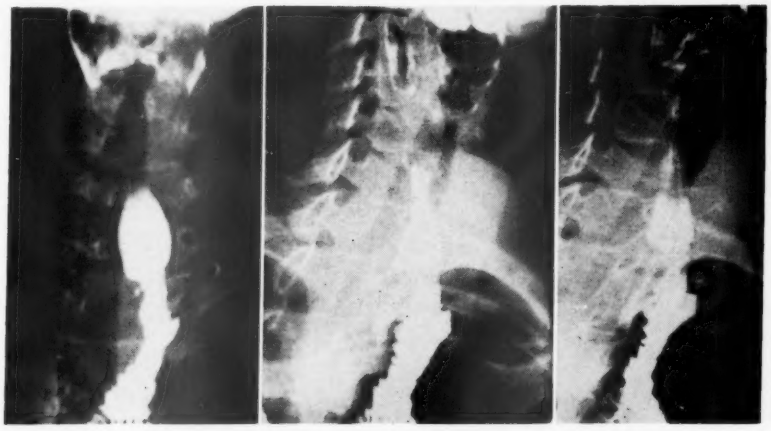
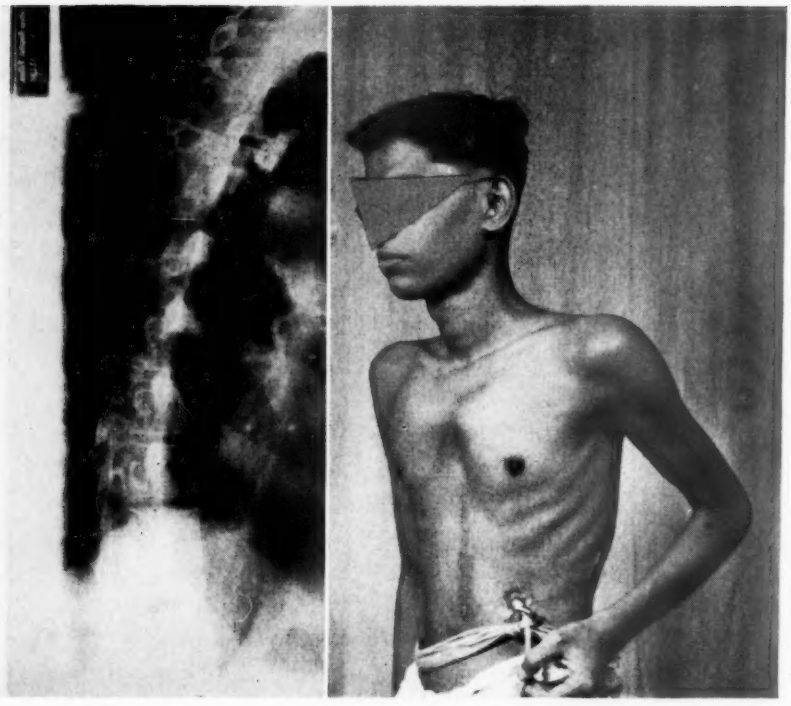
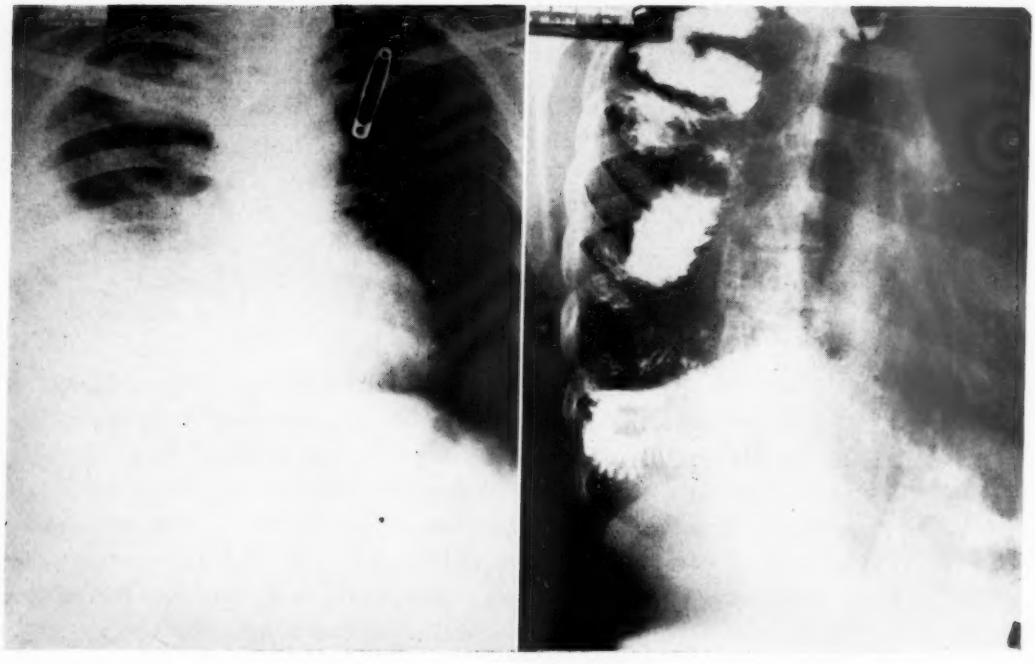


Fig. 1C.—*(For legend see opposite page.)*

apparently by Yudin[1] in practically every instance. There was marked temporary edema of the end of the jejunum in those cases in which we have had the opportunity to observe it. The edema regresses in a few days or a week. Presumably, a similar degree of edema is present in those cases that have had the anastomosis completed in a one-stage procedure. No doubt a safer anastomosis can be carried out one week or ten days later. We believe that this is the reason that we have had so many temporary salivary fistulas in our series of patients. With greater attention to the mobilization and especially with the use of an end-to-side anastomosis in the neck, we believe that the avoidance of the fistula may be possible in a larger percentage of cases and still complete the procedure at one sitting.



A. *B.*



C. *D.*

Fig. 2, *A-D.*—*(For legend see opposite page.)*

Provision of drainage through a stab wound in the lateral aspect of the neck is important. Although many of our cases have had a temporary salivary fistula at the site of the anastomosis, all have healed spontaneously, except in the one instance where the segment sloughed. The apparent innocuousness of this leakage is surprising and, no doubt is due in great part to the use of antibiotics.

E.

Fig. 2.—Case 8. Mr. V. K. R. was admitted to the hospital's Ear, Nose and Throat Service two months after swallowing an estimated one-half ounce of nitric acid with suicidal intent on Jan. 25, 1954. Repeated attempts to provide an adequate esophageal lumen by dilatations were unsuccessful and a gastrostomy was carried out for feeding purposes, after which he was tranferred to the Thoracic Surgical Service.

A, The patient was so completely obstructed that he could not swallow his saliva, and a barium swallow on July 21 demonstrated almost complete esophageal occlusion just at the level of suprasternal notch. The patient had a marked pectus excavatum, as shown in *B*. Due to this deformity, it was not possible to bring the segment of jejunum up through the anterior mediastinum. The right transthoracic route was therefore used and the jejunum taken posterior to the trachea and out into the left cerivcal region where the anastomosis with the proximal esophagus was carried out. An end-to-side anastomosis was performed. Operation carried out in one stage on July 31. *C*, In the immediate postoperative period the patient had severe pneumonia on the right side due to aspirated saliva as he was still not able to swallow all of this material in the early postoperative period. Although the x-ray appearance is suggestive of pleural fluid, it could not be aspirated, and the infiltration cleared rapidly on antibiotic therapy without the removal of any fluid. *D*, Postoperative roentgenogram showing the jejunum traversing the right hemithorax. *E*, Spot film demonstrating the jejunum crossing posterior to the trachea and the cervical esophagojejunostomy.

We have had no real worry about getting any of these patients through the operation itself, but several have given us concern during the postoperative period, and this has always been due to the problem of excessive pulmonary secretions and infection. Many of these patients before operation had been so obstructed that they could not swallow their saliva and, consequently, it was aspirated into the bronchi causing frequent bouts of pulmonary infection. After operation, in spite of an adequate anastomosis, they often can-

not swallow saliva for several days, and periodic tracheobronchial catheter aspirations are necessary. In one or two instances, quite severe pulmonary infections ensued which in each case fortunately terminated favorably, due to antibiotic therapy.

When this operation was first proposed, grave doubts were expressed that it would be possible to maintain adequate nutrition inasmuch as the stomach is sidetracked. In the report of Yudin,[1] he anastomosed the distal end of the jejunal segment to the stomach. This is also the plan advocated by Harrison,[4] but Robertson and Sarjeant[3] found that it was usually not necessary.

A. *B.*

Fig. 3.—Case 9. Mr. K., a goldsmith, was admitted to the hospital on July 24, 1954, six weeks after he is stated to have been forced to swallow 1 ounce of nitric acid by a dissatisfied customer. Increasing difficulty in swallowing developed, but he could still swallow some of his saliva at the time of admission. A gastrostomy was performed four days after admission. *A*, Appearance of esophagus after a swallow of Lipiodol on July 28. At esophagoscopy, the mucosa was found to be inflamed, beginning 2 cm. below the cricopharyngeus, but the obstruction was not acute until a distance of 23 cm. from the upper incisor teeth was reached. It was deemed unwise to attempt surgical repair until this inflammation had subsided. Esophagoscopy was repeated on August 25, and the reaction was much less acute. A Robertson-Sarjeant type of repair was done in one stage on September 11. *B*, This oblique view demonstrates the jejunum traversing the anterior mediastinum. *C*, This shows the anastomosis in the cervical region and demonstrates the use of the redundant portion of the jejunum for the anastomosis by the end-to-side method, thus lessening the tension on the limiting vascular arcade.

Sweet,[3] in discussing the paper of Robertson and Sarjeant, said that he also had had difficulty in maintaining the patient's nutrition when the stomach was by-passed. This has not been true of our patients and, in every instance, they have gained weight rapidly as soon as they were able to eat in a normal fashion, and, in the ones that we have had the opportunity of following, there

has been no evidence of any anemia developing. The gastric secretions, of course, are not lost in this type of operation, but the storage function of the stomach has to be taken over by the jejunum, and the gastric secretions only come in contact with the ingested food lower down in the intestinal tract. A recent report by Mekie[21] stated that maintenance of nutrition has not been difficult in his cases following an intrathoracic sidetracking operation by the use of a Roux jejunal segment.

We have not encountered in the literature any recorded experiences concerning the time when the esophageal reconstruction should be performed. In those cases where there is sufficient normal esophagus above the stricture,

Fig. 3C.—*(For legend see opposite page.)*

there apparently is no necessity for waiting. Burford, Webb, and Ackerman[24] reported two cases which were performed approximately six weeks after the injury to the esophagus. In those instances, however, the stomach was brought up and anastomosed to apparently normal esophagus above the strictured site. Our last two cases have presented a bit different problem as both were seen fairly soon, that is, within a few weeks of the time of the ingestion of the chemical and before the fibrotic process in the esophagus had gone on to its final stage. In both instances, esophagoscopic examination revealed that the mucous membrane was not normal from the cricopharyngeus down to the point of stricture. It was believed that if esophagojejunostomy were performed before the reparative process was complete, fibrosis and shrinkage might result in poor healing of the anastomosis or stricture formation later on. That the process does continue for some time was evidenced by repeated esophagoscopic examinations in these two cases, which showed that the point

of stricture was measured at progressively shorter distances from the upper incisor teeth during the first two to three months after injury. Even at the time of the esophagojejunostomy in these last two cases, the mucosa of the esophagus was not normal at the point of anastomosis, but there had been no change in the appearance between their last esophagoscopic examinations and, therefore, it was felt permissible to go ahead with esophageal reconstruction. In both of these instances, a period of almost three months was necessary after injury before the lesion seemed stable enough to proceed with definitive surgical treatment.

The management of extensive esophageal strictures is likely to be difficult by any method. We are reporting our cases to show the various problems and complications that were encountered. It is believed that with increasing experience most of the complications should be eliminated.

SUMMARY

1. Extensive benign esophageal strictures have posed a challenge to surgeons for many years, and a short survey of the methods proposed and used for their correction has been enumerated.

2. The Robertson-Sarjeant procedure of substernal extrapleural jejunal transplantation for cervical esophagojejunostomy seems to us the best method so far proposed to provide a substitute esophagus. Its advantages and disadvantages are set forth.

3. Our experience in treating nine cases of extensive benign esophageal strictures, by the Robertson-Sarjeant technique in eight and transthoracically in one, is presented. Although a number of major complications were experienced, there were no deaths in the series, but one jejunal segment was lost.

ADDENDUM

At a meeting of the Association of Surgeons of India at Hyderabad, India, on Jan. 1, 1955, Prof. B. A. Petrov, of Moscow, who now holds the chair formerly occupied by Yudin, reported on "Surgery of Reconstruction of the Gullet." He stated that 313 corrosive strictures of the esophagus were treated surgically by Yudin and that during the last five years, since the death of Yudin, he had treated 321 more cases, or a total of 634, with an operative mortality of 4.3 per cent. The procedure now used is that described by Robertson and Sarjeant, which operation Petrov stated was originally developed by a Russian surgeon, Eremeev, of Omsk, in 1946! Petrov has now performed 25 such operations with three deaths. The operation is always performed in two parts with the cervical esophagojejunostomy being carried out about one week after the mobilization of the jejunum.

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THE SIMULTANEOUS HOMOTRANSPLANTATION OF MULTIPLE SKIN GRAFTS

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MEDAWAR[1] has stressed the importance of the dosage of skin in relation to the survival of homografts. His experience with rabbits showed a direct relationship between size of dose and speed of disintegration. Dempster,[2] also using rabbits, reported that multiple skin homografts, having a combined weight of 0.9 gram and over, are dead within four days. This worker postulated that "dosage factor may be confined to skin, as it is certainly not an important factor in homotransplanting kidneys."

Our investigations are at present confined to a study of homografted skin on mice. In view of the previously reported results of skin homografting in a different species, it would be of interest to determine any similarities or dissimilarities. We have set up this series of experiments utilizing graded doses of homografted mouse skin.

One hundred thirteen 6-week-old CFW mice, each weighing approximately 20 grams, were employed in these experiments. Two, three, or four full-thickness skin grafts were transplanted simultaneously on each mouse. Each homograft weighed approximately 0.08 gram. Fig. 1 shows the various positions of these grafts on the recipient.

In the two series of mice, each recipient received multiple homografts from one or several donors. The technique of applying skin grafts and the criteria for determining viability has been previously described by us.[3] The grafted mice were observed at daily intervals and, at the time of writing, had been observed for at least five months.

RESULTS

A total of 338 homologous skin grafts were transplanted on 113 heterozygous CFW mice. Seventy-eight of these grafts were transplanted two at a time to each recipient; 108 grafts, three at a time; and 152 grafts, four at a time. The number of recipients which received homologous skin grafts from one donor and multiple donors were approximately equal.

Table I contains results which demonstrate a relatively more rapid rate of necrosis when multiple grafts were transplanted. When a single homograft is transferred, necrosis has begun by the tenth day. When two to four grafts are transplanted to a single recipient, necrosis is evident in all the grafts within five to nine days. The average time interval for beginning necrosis for the multiple grafts obtained from a single donor is six days and from different

Supported in part by United States Public Health Grant C1827.
Received for publication Feb. 14, 1955.

donors is seven days. This clearly demonstrates that multiple or single donors produce essentially similar results. Also, it is shown that multiple grafts initiate a more rapid appearance of necrosis than single grafts.

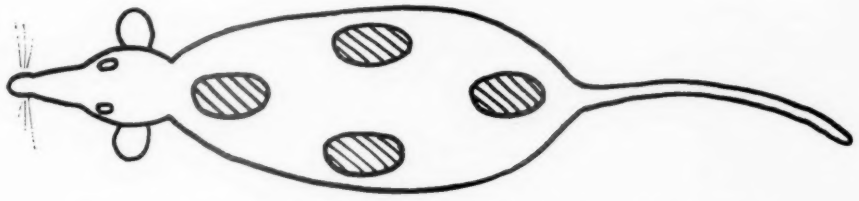

Fig. 1.—Anatomical location of maximum number of homografts.

However, if the skin grafts are observed over a longer period, say ninety days, entirely different results become evident. In Table II it can be seen that seven grafts had remained viable. The superficial necrosis of the epidermis in a skin graft is a constant observation. Prolonged observation of such grafts will seven recipients. Six of these occurred on animals receiving multiple transplants have been missed if a small number of animals were used and not observed for an extended time period.

TABLE I. OBSERVED TIME INTERVAL BETWEEN HOMOGRAFTING AND THE APPEARANCE OF NECROSIS

NO. OF GRAFTS PER MOUSE	TOTAL NO. OF GRAFTS	DONORS	BEGINNING NECROSIS IN ALL GRAFTS (DAY)
1	124	Single	10th
2	36	Same	7th*
	42	Different	7th
3	54	Same	5th
	54	Different	9th
4	80	Same	6th†
	72	Different	5th†

*Excluding 3 viable grafts.
†Excluding 1 viable graft.

TABLE II. VIABILITY OF HOMOGRAFTS AT 150 DAYS

NO. OF GRAFTS PER MOUSE	TOTAL NO. OF GRAFTS	DONORS	NUMBER OF VIABLE GRAFTS
1	124	Single	0
2	36	Same	3
	42	Different	0
3	54	Same	0
	54	Different	0
4	80	Same	3
	72	Different	0
Total	170	Same	6
	168	Different	1

DISCUSSION

The transplantation of 338 multiple homografts resulted in viable grafts on seven recipients. Six of these occurred on animals receiving multiple transplants from a single donor, and one occurred on a recipient which received multiple transplants from four different donors. In all seven instances, the anatomic

location of the viable grafts was at the superior dorsal area. Autografts transplanted to the same anatomic area resulted in permanent growth. Skin grafting to any other body area was unsuccessful because of inability to stabilize the skin graft, excessive motion, and the destruction of the graft by chewing.

The results indicate that dosage may be an important factor affecting the behavior of skin homografts. In a recent review article, Snell[4] discussed the enhanced susceptibility of (1) mice to tumor transplants by either pretreatment with killed tissue, or by repeated tumor grafts; (2) mice to pneumococci by relatively large doses of killed bacteria, or bacterial polysaccharides; and (3) dizygotic twin calves to skin homografts by pretreatment in utero of massive doses of blood. These different phenomena, as well as the results presented in this report, may be fundamentally similar. In addition, we have found that repeated homografts[5] and injection of skin extracts[6] produced viable homografts in mice. The mechanism responsible for all of these observations may be explained by the phenomenon of "immunoparalysis."[4, 7, 8]

Medawar[1] and Dempster[2] have reported their findings on the use of multiple skin grafts in rabbits. However, these workers did not observe the transplants beyond a ten-day period and their dosage of skin, maximum of 0.9 gram for a 2,500 to 3,000 gram rabbit, was much less than that used in our experiment, that is, maximum of 0.3 gram for a 20 gram mouse.

CONCLUSIONS

Simultaneous transplantation of multiple skin homografts on CFW mice resulted in necrosis of the transplanted skin much sooner than that observed in transplanted single homografts. The results were nearly identical when either single or multiple donors were used. With an extended observation period of 120 days, it became apparent that 7 out of 338 homografts had remained viable. Only one of these was on a recipient which had received homografts from multiple donors. In contrast to this, all 124 single skin homografts became necrotic by the tenth day and none has been observed to survive.

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Case Reports

INSIDIOUS THROMBOTIC OCCLUSION OF CERVICAL CAROTID ARTERIES, TREATED BY ARTERIAL GRAFT

A Case Report

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THROMBOSIS of the cervical carotid arteries is being recognized with mounting frequency as the cause not only of strokes previously thought due to thrombosis of intracranial vessels, but, in addition, of rapidly or slowly progressive syndromes featuring aphasias, extremity sensory disturbances, hemipareses, monocular blindness, and hemianopsias—syndromes sometimes preliminarily considered due to neoplastic disease.[2, 5, 6, 9, 10, 11, 12, 13, 15, 16] No doubt, many occurrences of this lesion are daily undergoing diagnostic scrutiny and even necropsy examination without being recognized, since usually the neck vessels are not examined. It is probable that carotid artery occlusions account for a generous portion of the encephalomalacias due to undetermined cause reported in most series of autopsies on brain vascular disease (12.2 per cent of the 329 cases of Adams and Cohen[1]). Cervical carotid occlusion is probably important etiologically in the development of cerebral vascular insufficiency delineated by Corday, Rothenberg, and Putnam[3] and a more frequent cause than "spasm" of transient losses of cerebral function in a variety of circumstances.

The generally expressed attitude in numerous recent reports is that this condition may be strongly suspected on clinical grounds but is diagnosable, for certain, only by arteriography.[2, 5, 11, 12, 13] Thomas and Petrohelos[14] have demonstrated rather convincingly the utility of retinal artery pressure determinations in the diagnosis of unilateral carotid occlusions.

Treatment in the hands of most authors has been quite conservative, consisting of measures which, it was hoped, would produce significant vasodilatation and utilization of anastomotic channels. Thromboendarterectomy, described in a recent publication,[12] was unsuccessful. Eastcott, Pickering, and Rob,[4] in November, 1954, reported the successful resection of an occluded segment of the internal carotid with reconstruction by direct anastomosis of the internal to the common carotid. This patient was cured of recurring attacks of transient hemiplegia. In general, however, surgical intervention on the cervical carotid vessels with a view to re-establishing competent circulation through them seems not to have gained wide acceptance as yet.

Bilateral occlusion of the cervical carotid vessels is, according to Frövig[7] and Frövig and Löken,[8] an extremely rare condition, with but ten reported

Received for publcation March 14, 1955.

up to 1951. In none of these was any surgical restitution of blood flow attempted. We wish to report a patient with bilateral, cervical carotid artery thrombosis which was treated by bilateral arterial graft.

CASE REPORT

The patient, O. H. S., a 49-year-old man, had had three months of small spells described as "blackouts" attended by mild weakness of right leg, speech disorder, paresthesias in right hand, and, finally, constant motor aphasia. Occlusion of proximal left internal and common carotid arteries was proved. Carotid graft was accomplished with postoperative angiographic demonstration of patency of the graft. The patient recovered a portion of neurological function, but several months later he again deteriorated. Examination revealed that the left carotid artery through the area of graft was pulsating vigorously but the right carotid vessels were occluded. Right carotid arteries were exposed and graft substituted with reversal of neurological deficit.

The patient was first seen on July 7, 1954,* because of weakness in the right arm and leg and aphasia. Three months previously the patient noted the occurrence of two brief periods described at the time as "blackout spells." These episodes of transitory blindness or loss of consciousness lasted but a few seconds. He continued at work as a painting contractor but had repeated spells of some sort of unknown frequency. On one occasion, he was observed leaning against a post, and it was said that for just a moment the patient slid down toward the floor while in contact with the post and that during this period he had a blank look. He quickly regained control and appeared completely well. Shortly thereafter, the patient began complaining of weakness in either the right leg or both legs (it is not certain which). Around the first of July, 1954, he was observed to have some alteration in speech so that he talked as though intoxicated. At that same time, he began complaining of numbness in the right hand and gave evidence of poor and clumsy use in this hand. During the first week in July, all of these complaints increased and, on July 6, he became unable to speak at all.

On examination, he was noted to be a slightly obese, florid-appearing, aphasic man who apparently had excellent understanding of everything said to him. He was unable to speak except for the words "No" and "Ha." External examination of the head was unremarkable. There was no bruit audible nor was there any stiffness of the neck. The right carotid vessels pulsated in a normal manner, but on the left side the pulsation was distinctly inferior in vigor, and high up under the angle of the jaw no pulse could be felt at all. Brief compression of the right common carotid artery produced dizziness and approach to loss of consciousness with twitching of the right upper extremity. An attempt at palpation through the mouth was made and it was believed that pulsations were absent in the left tonsillar fossa, but the examination was extremely brief because of the gagging induced. Tests of gait and station were normal. The visual fields were full. The fundi were without abnormality. The upper portion of the face was symmetrical but the right side, about the mouth, was weak. There was apraxia of tongue and mouth movements and the patient perseverated in these movements. The right trapezius was weak. Grip in the right hand was distinctly weak and, in this hand, he manipulated objects poorly. Left tendon reflexes were more active than those on the right. No clonus or pathologic toe reflexes were present. Vibratory appreciation on the two sides was equal. The patient was unable to determine what objects were placed in the right hand, and, in finger-to-nose testing, performance was poorer on the left than on the right. All vessels of both upper and lower extremities possessed normal pulsations.

Roentgenogram examination of the skull revealed a calcified pineal in its normal midline position. There was no bony abnormality. Examination of the cerebrospinal fluid revealed an initial pressure of 179 mm. The fluid was clear and colorless and contained 66

*At the request of Dr. W. S. Duty.

mg. of protein. Electroencephalography* revealed an 8½ to 10 per second dominant occipital rhythm mixed with some moderately low voltage 15 to 20 per second activity. There was marked temporal asymmetry with fairly continuous episodes of moderately low to high voltage

Fig. 1.

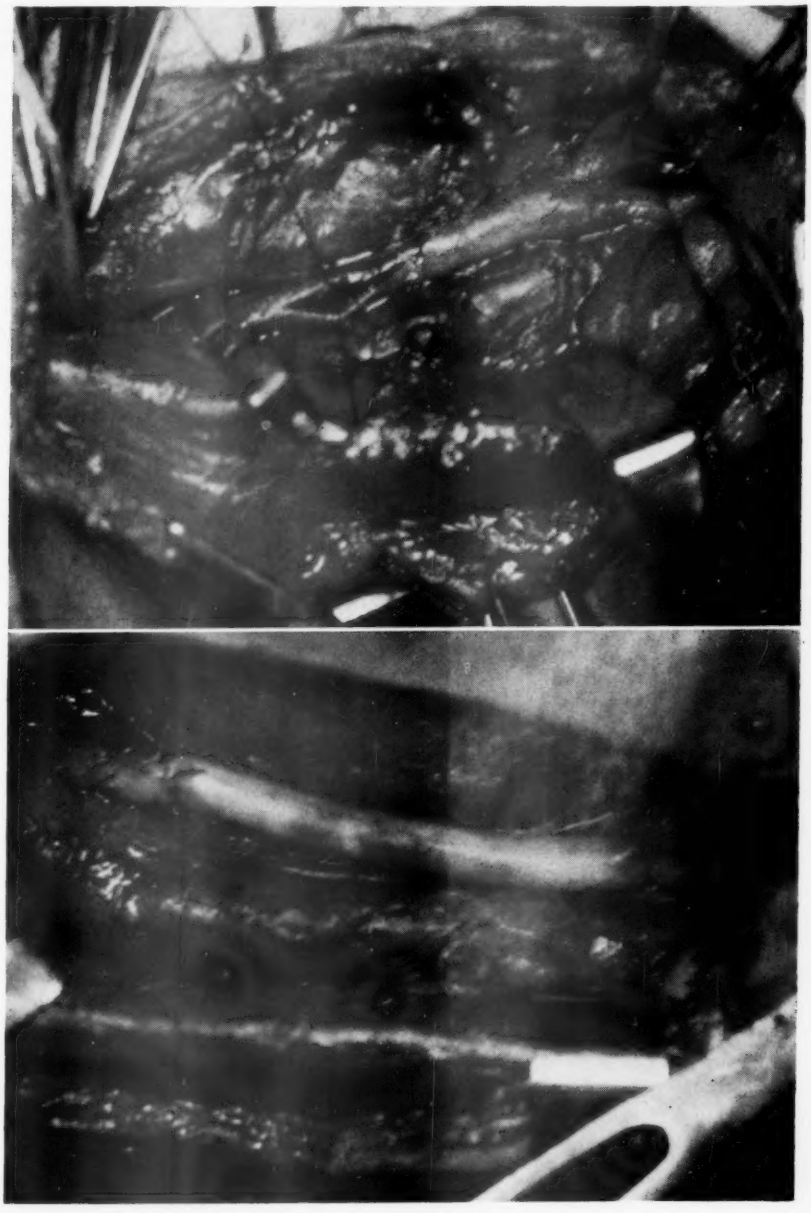

Fig. 2.

Fig. 1.—Left carotid artery showing thrombus.
Fig. 2.—Homologous arterial graft between left common carotid and internal carotid arteries.

3½ to 5 per second waves in the left temporal region, occasionally reflected to a much lesser degree and at much lower amplitude in the left frontal region. Hyperventilation produced

*By Dr. Peter Kellaway.

some slight increase in the left temporal slowing. These findings were considered* to point to the existence of a slow wave focus in the left frontotemporal region, probably on the basis of ischemia.

A diagnosis of occlusive disease of the left internal carotid artery, producing left hemisphere ischemia, was made.

It was believed, prior to exploration of the carotid artery in the neck, that pneumoencephalography should be conducted to obviate any possibility of there being a space-taking lesion present. On July 13, 1954, this was made, revealing ventricles of normal size in normal positions. The amount of subarachnoid air was perhaps slightly increased but not sufficiently to suggest definite cerebral atrophy.

Fig. 3.—Carotid angiogram showing functioning arterial graft (arrows) and normal cerebral circulation.

Whereas, at first, the common carotid artery could be palpated bilaterally, by July 13, this pulsation had disappeared on the left. For this reason, preliminary arteriography was not performed since we felt that this indicated proximal extension of the thrombus.

Accordingly, on July 14, the left carotid vessels were explored. A vertical incision was made along the anterior margin of the left sternomastoid muscle, and the common carotid, internal carotid, and external carotid arteries were exposed by appropriate dissection, being careful to protect the vagus and superior laryngeal nerves and the internal jugular vein. The internal carotid artery was isolated to the base of the skull. At the carotid bifurcation, there was a palpable calcified atherosclerotic plaque. There was no pulsation in any of the vessels. A longitudinal incision, 2 cm. long, was made in the common carotid just below the plaque and a soft red thrombus was encountered extending to the aortic arch.

*By Dr. Peter Kellaway.

This was readily removed by suction and a gentle milking action until a forceful free flowing stream of blood surged upward from the aortic arch. A bulldog clamp was applied. The internal carotid was soft and pliable from just beyond the atheromatous plaque which extended

Fig. 4.—Right carotid arteries showing thrombus.

Fig. 5.

Fig. 6.

Fig. 5.—Resected carotid bifurcation and thrombus.
Fig. 6.—Resected specimen opened to show obstruction by arteriosclerotic process.

1 cm. distal to the bifurcation. The distal 2 cm. of the common carotid, the carotid bulb, and the proximal 2 cm. of the internal and external carotid were resected. The external carotid was ligated. There was a nonpulsatile flow of blood returning from the internal carotid. A lyophilized arterial graft was inserted between the common and internal carotid arteries using interrupted everting sutures of fine silk. After releasing the bulldog clamps, pulsations were visible and palpable through the internal carotid until it disappeared at the base of the skull. An arteriogram was made by injecting 10 c.c. of 30 per cent Urokon into the common carotid artery demonstrating the graft and restoration of normal intracerebral circulation through the anterior and middle cerebral branches of the internal carotid. The incision was closed with interrupted fine silk and the wound was drained. Heparin 100 mg. was given intravenously by the anesthesiologist, and heparinization was continued in the postoperative period for ten days.

Fig. 7.—Homologous arterial graft between right common and external carotid arteries.

On opening the resected carotid bifurcation, the previously felt atheromatous plaque was seen to have completely obstructed the orifice of the internal carotid. Apparently, a crack developed which the current of blood dissected cephalad as a flap to effect complete occlusion.

By July 18, the patient was up and about his room and was reading the newspapers, seemingly with understanding. The right hand was quite paretic and proximal parts of this extremity possessed more power than the distal. The patient made grunting sounds but had no speech. The next day, the grip was distinctly improved and on hospital dismissal, July 20, was still better. At that time, a strong pulsation could be felt in the carotid vessels through the area of the graft. Though the patient had no speech, he was able to project his tongue much better than prior to the operation, due to diminution in apraxia.

The patient was examined again on August 28, at which time his wife stated that he was able to copy any printed or written material and that his arithmetic skills were normal. He had had no seizures of any kind and had demonstrated increasing function in the right arm. His speech was limited to the words "No" and "Ha." He had no complaints except for what seemed to be abnormal sensation in the left side of his face. On examination, the patient demonstrated full visual fields with normal ocular fundi. There was no weakness in the face, whatever. There was still some slight paresis of the trapezius on the right.

He was able to project the tongue quickly on request and could wiggle it from side to side without any evidence of the severe apraxia of this movement which he had previously had. There was some diminution of grip in the right hand and a little slowness in wiggling the fingers but these functions were distinctly better than they had been preoperatively. The tendon reflexes were active and equal on the two sides and there was no pathologic reflex in the feet. Sensation on the two sides was normal. The patient was able to write his name, although this act was carried out with slowness and deliberation. After conclusion of the writing, he dropped the pencil and in picking it up used his left hand. He was said to carry no keys or coins in his right pocket because of difficulty in grasping them and identifying them. A vigorous carotid pulse was present in the left side of the neck through the site of the graft.

The patient was seen again on October 2, a little over one month following the prior examination and almost three months following his surgery. It was stated that prior to four days before this examination he had had complete return of feeling and use in the right hand but that it had recently become numb and that his handling of small objects was distinctly poorer. It was said that he could still write but that the grip of the hand was weak. No abnormalities had appeared in the legs. The patient was still unable to speak. On examination, visual fields and fundi were normal. Motor function in the right extremity was moderately reduced. Vibratory appreciation was equal on the two sides but position sense was poor on the right. Tendon reflexes were active and equal. A strong left carotid pulse was still palpable, but on the right side no pulse whatever could be felt.

The patient was readmitted to Hermann Hospital, and, on October 10, a similar operation was performed on the right carotid vessels. At operation, however, the internal carotid artery was found to be obliterated by an organized thrombus and atheromatous intimal and medial thickening all the way to the base of the skull. The external carotid was patent and an arterial graft was inserted between it and the common carotid. Restoration of the external carotid circulation was considered desirable primarily because of its communication through the ophthalmic artery with the circle of Willis.

The patient was again heparinized and this time Dicumarol was given to maintain long-term anticoagulant therapy. There was almost immediate improvement in the functional capacity of the right upper extremity, and on dismissal from the hospital on the sixth postoperative day, he had improved to the function level obtained just before his relapse. Since this time, he has been gradually improving in his ability to speak; however, at present (four months postoperatively), he can speak only single words.

DISCUSSION

The case presented illustrates the occurrence of segmental arteriosclerotic occlusion of the internal carotid artery as a cause of cerebral vascular insufficiency, varying in degree from the classic "stroke" to transient episodes of "blackout" spells, blindness, extremity motor and sensory disturbances, or aphasias.

Pathologically, the internal carotid artery is involved by a localized arteriosclerotic process which produces gradual narrowing and final occlusion due to thrombosis. Usually this occurs at or within 1 cm. of the carotid bifurcation and is followed by both distal and proximal extension of the thrombus with eventual organization.

It is our belief that a significant number of patients with either minor or major strokes are being misdiagnosed as cerebral thrombosis or hemorrhage. We consider the distinction important because, whereas little, if any, definitive treatment is possible for the latter, prompt recognition and treatment of internal carotid occlusion may rapidly improve the neurological deficit and prevent further deterioration.

The diagnosis must first be suspected. Palpation of the carotid arteries high under the angle of the mandible and of the internal carotid arteries behind the tonsillar fossa after anesthetizing the pharynx will reveal the absence of pulsations on the involved side. Compression of the opposite carotid artery will result in blanching of the retinas and may provoke some gross neurological feature. Carotid angiograms will reveal a block near the carotid bifurcation.

Ideal surgical therapy consists of extirpation of the diseased part and restoration of function. This objective may be realized in this condition, if as with other forms of arterial occlusion, the diagnosis is made and surgery performed before extension and organization of the thrombus have progressed too far. Ischemic damage to brain tissue may not be reversible and, since it occurs rapidly, may not be preventable; however, restoration of normal carotid arterial flow by resection of the occluded area and arterial graft may well prevent further progression of the lesion and forestall greater deterioration of the patient. If angiographic diagnosis and restorative surgery are performed while patients are still in the clinical phase of cerebral claudication (transient faintness, dizziness, sensory disturbances in an extremity provoked usually by exertion) and before irreversible brain cell damage occurs as a result of total occlusion, excellent functional results can be expected, as exemplified in the case of Eastcott, Pickering, and Rob.[4]

SUMMARY

1. Attention is called to arteriosclerotic segmental occlusion of the internal carotid artery as a cause of certain neurological syndromes simulating a stroke.

2. A case of bilateral internal carotid arteriosclerotic occlusion is reported in which bilateral arterial grafts were inserted in order to restore normal cerebral circulation.

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PARTIAL OCCLUSION OF TERMINAL AORTA COMPLICATED BY SUDDEN TOTAL OCCLUSION

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RESECTIONS and replacement of the distal abdominal aorta are now being carried out with increasing frequency.[2, 3, 6, 8, 12] The circumstances under which the following case was performed, however, seemed sufficiently unusual to warrant reporting.

This patient's clinical picture suggested a massive arterial embolus at the bifurcation of the aorta whereas extensive disease had been present for a long time, and then minor additional occlusion precipitated the acute picture.

CASE REPORT

W. G. was admitted to the Hospital of the University of Pennsylvania on Oct. 14, 1954, at 6:30 A.M. because of intense pain in his left leg. This 52-year-old man was in Philadelphia on a business trip and had been in his usual state of health until 11:30 P.M. of the night before admission, when he suddenly experienced mid-abdominal pain, followed by copious vomiting. Relatively soon thereafter, he developed a watery diarrhea which lasted until 2:30 A.M. when it subsided, and he was able to fall asleep. At about 3:00 A.M. he was awakened by very severe pain in the left hip and leg. The pain was constant and progressive and quickly involved the entire limb. After suffering for a considerable time, he called Dr. Simon Leopold who made a tentative diagnosis by telephone of an arterial embolus and arranged for the patient's immediate admission to the Hospital of the University of Pennsylvania.

On admission, the patient gave a history of intermittent claudication of three years' duration, both legs being affected, but the worst trouble having occurred in the right leg. He could walk only a block, or occasionally two blocks, without pain. Because of this difficulty, he had been studied at Duke University Hospital two years earlier, and a sympathectomy had been advised at that time, but the patient had declined operation. The claudication had not changed materially in the following two years and was not associated with sexual difficulties. To the best of his knowledge, he had never been hypertensive, nor did he have heart disease. He had, however, had two episodes of blurring of vision associated with defects in his visual fields. These episodes had partially cleared spontaneously several weeks after their occurrence. He had smoked one and one-half packs of cigarettes a day for thirty-five years, but otherwise his history was noncontributory.

Physical examination on admission revealed the patient to be a well-nourished man in intense pain. He looked to be his stated age. The blood pressure was 200/110, the pulse was 88, and respirations, 18. The chest was clear. The heart was of normal size, and there was normal sinus rhythm; a harsh grade II systolic apical murmur and a grade I diastolic murmur in the aortic areas were audible. Abdominal examination revealed a soft abdomen without masses. A right inguinal hernia was present.

The unusual findings were restricted to the legs. The left leg was cold from the groin down, and from the knee down was very pale, appearing practically cadaveric. The left foot was totally anesthetic. He could, however, still move his toes a little. There was no pulse palpable anywhere in this leg. The right leg was of normal color, but distinctly cool.

Received for publication March 14, 1955.

When first seen, no pulses were palpable in this leg either, but, within thirty minutes, a very faint femoral pulse became palpable. There was no anesthesia nor loss of motion in this leg, and it did not hurt him.

At 7:50 A.M. while the patient was being observed, a flare suddenly developed in the left leg and extended down to the foot. Sensation, however, did not improve, nor was there any return of pulses. A left lumbar sympathetic block was carried out a few minutes later without having significant effect on the objective findings. It, however, gave slight subjective relief of pain.

Laboratory studies at this time revealed a hemoglobin of 121 per cent or 18.8 Gm. His white blood count was 17,300, and the urinalysis showed a trace of albumin, many white cells per high-powered field, and a few casts. Blood for blood urea nitrogen and fasting blood sugar determination was drawn, and both were reported to be within normal limits later in the day.

A diagnosis of saddle embolus or thrombosis was made, and operation decided upon. The possibility of his having had a thrombosis occurring on the basis of polycythemia was considered, but this possibility was later found to be incorrect.

The operation was started at 10:00 A.M., and the abdomen entered through a midline incision. The bowel was packed off, and the aortic bifurcation exposed with the two common iliac arteries. There was no pulsation in the terminal aorta which felt firm up to a point just below the inferior mesenteric branch. The right common iliac was very firm, and clearly occluded by an old process. The left common iliac, although sclerotic, did not feel solidly occluded. After isolating these vessels, and getting a clamp about them, the aorta was opened just above the bifurcation and a fairly fresh clot removed. It was rather small and clearly indicated that the lumen of the aorta which it blocked was small at that point. After closing the aorta and releasing the clamps, a pulse returned to the aorta and to the left common iliac artery, but none could be felt in the right common iliac, or either of the external iliac arteries, and none could be felt in the left leg.

An incision was then made over the left femoral artery which was exposed at the point where the profunda femoris arose. After occluding the common, superficial, and deep femoral arteries, the common femoral was opened, but no clot was found at this point. An intraluminal vein stripper was then passed down the vessel as far as the lower part of the popliteal without meeting obstruction. Following this, it was passed up the vessel and met an obstruction at the point of the bifurcation of the left common iliac artery. With the abdomen open, the stripper and the point of occlusion could be readily felt in this area. The decision was then made to resect the aorta and common iliacs and put in a freeze-dried arterial homograft. Such a graft was reconstituted while the femoral vessel was closed and further dissection carried out in the abdomen. The right external and internal iliacs were then exposed and transected about 1 cm. below their bifurcation, and, although they both had some sclerotic changes, fairly good retrograde bleeding was encountered. There was no bleeding from the proximal end of these vessels. The left internal and external iliacs were then also divided in the same area and again retrograde bleeding was obtained. The aorta was severed just below the inferior mesenteric branch. The aorta itself was not particularly healthy at this point, but its lumen was not encroached upon. The graft was then sutured in position using No. 4-0 Deknatel silk sutures for the aorta, and No. 5-0 Deknatel for the iliacs. The aorta itself was first sutured, and as each of the iliac branches were sewn, blood was allowed to flow through that vessel. Thus, both the internal and external iliac arteries were sutured on both sides. After completion of these anastomoses, a good pulse was felt throughout the graft, but the left femoral artery still did not have pulsations. The femoral artery was, therefore, again opened by removing the sutures which had previously been placed in it, and several small fresh clots were found and removed. This vessel was then again closed, following which it developed a palpable pulse.

The left lumbar sympathetic chain was then exposed at the level of the fourth lumbar vertebra, and a segment of the chain, including two ganglia, was removed. The posterior peritoneum was then closed over the graft, and the abdomen closed without drainage. The wound in the femoral area was also closed and the operation completed.

In the recovery room, the dorsalis pedis was palpable in the right foot, and the right leg appeared to be in fine condition. The left leg, however, although improved, was not good. It had become warm down to the calf, and its color had improved, but the toes remained cold and relatively bloodless. No popliteal nor pedal pulse could be felt.

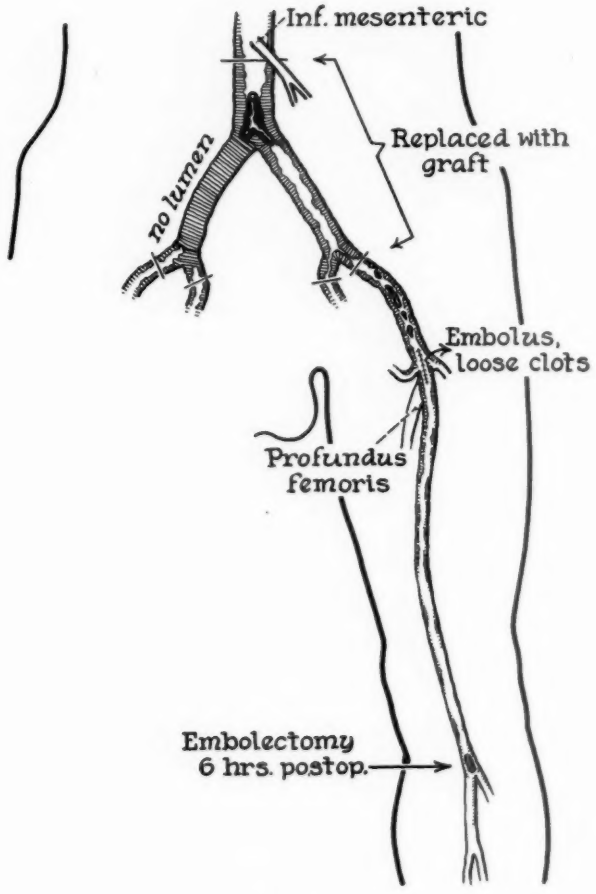

Fig. 1.

A 10:00 P.M. on that evening, both a dorsalis pedis and posterior tibial pulse could be felt on the right side. The left leg had improved a little more, but still was without a pulse below the femoral, and four of the five toes appeared to be very cyanotic and looked as if they would probably definitely demarcate before too much longer. It was, therefore, decided to open up the left popliteal artery and see if we could not remove an obstruction at this point. This operation was started at 10:50 P.M., more than sixteen hours after the patient's admission to the hospital. With the patient in the prone position, general anesthesia was again used, and an incision was made over the left popliteal artery. Having been isolated, this vessel, which was not pulsating at that time, was opened and found to bleed very little. The intraluminal stripper was, therefore, passed proximally and, when withdrawn, was followed by a good stream of blood with a few fresh clots which had been dislodged. A probe and suction tip were then passed about 7 inches distally down the vessel, and some retrograde bleeding thus obtained. The opening in the popliteal artery was then closed, and at completion of its closure, a palpable pulse was present throughout the vessel's length. Immediately after this operation, no distinct change was noted in the foot. Four hours later,

however, the foot was found to be greatly improved in color, warmth, and sensation. By then it appeared that the toes were viable, and that no loss of tissue would occur unless further trouble developed.

Papaverine, in a dose of 90 mg. every six hours, and antibiotics were started immediately postoperatively. Heparin was started on the first postoperative day. Although the left foot was much improved in appearance following the operation, no pulse was palpable in it until the fifth postoperative day when the dorsalis pedis was first felt. Three days later, the posterior tibial pulse became palpable. The right leg showed surprising changes. As mentioned, pulses were felt in the right foot immediately after operation and were palpable on the next day, but then they suddenly became impalpable, only to return four days later. This observation was confirmed by many people. Following this time, the pulses in both feet gradually became a little stronger over the next several weeks. Oscillometric readings at the ankle twelve days postoperatively were reported as "almost normal, smaller on the left side than right."

On the eleventh postoperative day, in spite of continuous heparinization, the patient developed definite signs of phlebitis in his left calf. He was treated by returning him to bed and continuing his anticoagulants, and the phlebitis gradually subsided over the next two weeks. A little swelling persisted, but this, too, has since disappeared.

So far as his general condition was concerned, his postoperative course was smooth. He was able to eat on the third postoperative day, and his temperature returned to normal on that day. His blood pressure, which had been 200/110 on admission, dropped soon after operation, and for a few days was a little below normal, and then gradually rose again to normal levels and stayed in the range of 120-130 systolic, 70-80 diastolic. His hemoglobin, which had been 121 per cent on admission, dropped into the range of 90 per cent when he became rehydrated. His serum cholesterol was found to be 271 mg. per cent, and a serologic test for syphilis was negative. His other laboratory studies were also essentially normal.

During this period of convalescence, ophthalmologic examination revealed a slightly incongruous left homonymous partial quadrantanopia. It was believed to have resulted from a vascular accident occurring in the optic radiations, presumably in the right parietal lobe.

The patient was discharged on Nov. 12, 1954, and a recent letter from him reported that he was in fine condition and walking without claudication.

Microscopic examination of the resected arteries showed atheromatous changes with cholesterol deposition, fibrin, and calcification. A few foci of bone formation were seen in the wall of the aorta and were accompanied by actual bone marrow.

DISCUSSION

Since Leriche[7] described, in 1923, the syndrome now bearing his name, this condition has been recognized with increasing frequency. Occlusive disease of the aorta had been recognized before,[16] but since the picture was highlighted by Leriche, many reports of this condition have appeared. Leriche himself said that replacement of the aorta would be the treatment of choice but felt that it was impossible at that time, that is, 1923. Sympathectomy and simple resection of the diseased vessel have been used up until recent times, but, within the last four to five years, more direct attacks have been made in some centers, both thromboendarectomy[17] and arterial grafts having been used. The usual clinical picture in these patients is one of gradually increasing claudication which is very apt to be first felt in the region of the hip and thigh. In those having complete occlusion of the aorta or both common iliac vessels, sexual impotence is a common finding,[8] but it is far less common in those with partial occlusion.

As a rule, partial occlusion will slowly progress over a matter of years. Collateral circulation usually develops to the point where trophic changes in the legs are not prominent, but ischemic necrosis may eventually supervene. The disease is usually found in men between the ages of 40 and 60, and, strangely enough, complete occlusion is apt to be found in a relatively young group. Sudden episodes of occlusion such as this patient had are not common and were not reported in several large series in the literature.[1, 3]

We may speculate as to why the sudden occlusion occurred, and it may be related to the straining and dehydration resulting from the diarrhea and vomiting. It seems unlikely that the gastrointestinal symptoms resulted from the occlusion inasmuch as pain in the legs was not felt until four hours after the onset of vomiting. We never had evidence to suggest that there had been a coronary occlusion or other intracardiac source of an embolus. It is possible that the clot formed higher up in the aorta, but in view of the relatively fresh appearance of the clot it is more likely that it formed in situ, probably having been precipitated by partial separation of a plaque.

In this patient, it is apparent that we could not have helped him if attempts to remove the thrombus had been made via the femoral arteries. In general, we feel that the direct approach to the site of a suspected embolus is desirable if the patient can withstand such a procedure. Here it was essential that the site of the block be exposed. An operation of this sort, however, requires large incisions, and considerable operating time, and may be too much for some patients to undergo.

In general, popliteal embolectomy has not been an extensively used procedure,[4, 14, 15] but, in this case, we believe it was responsible for saving at least part of the leg. Too often it is stated that the results of treatment of embolism are satisfactory if one simply does not lose tissue, but too little attention has been paid to function. The man who has an unrelieved popliteal arterial block is almost certainly doomed to at least severe claudication and, in a fair proportion of cases, to loss of at least part of his limb. Seven out of 33 cases reported by Warren, Linton, and Scannell[15] lost some part of their limb. The percentage of those having late ischemic symptoms is not given but must be very high. It is our belief that a more aggressive attitude toward popliteal emboli should be taken and that the preservation of useful function should be our criterion of success, not mere preservation of the foot. The hesitancy to undertake embolectomy in the popliteal artery that has generally been found in the past is surprising in view of the relatively easy technical procedure that it is.

It is also of interest that the popliteal embolectomy was not carried out until at least twenty hours after occlusion of the circulation of the leg. This confirms what others have found; namely, that late embolectomy may be successful if irreversible ischemic changes have not occurred in the limb. Olwin[11] and others[4] have reported successful embolectomy days after the onset of occlusion, and one cannot set an absolute time limit for operation. The time during which one may successfully perform an embolectomy will vary with the adequacy of the collateral circulation to the tissue distal to the block.

The delay in return of peripheral pulses following embolectomy is a curious phenomenon which we have observed in other cases also and the exact explanation for which we do not know. We presume that it is related to spasm in the arterial tree, although such is by no means certain. We have made some pressure studies on other patients above and below arterial grafts, immediately after they have been placed, and there have been profound drops in arterial pressure distal to the graft despite the fact that pulses were clearly palpable at that point. The possibility of small air emboli occurring with the insertion of the graft is obvious, and such might be factors of a temporary nature, effecting the distal pulse.

The eventual outcome of human arterial homografts will not be known for a good many years, for none has been in place for a long period of time. So far as we are aware, Gross was the first to use a human arterial homograft in February, 1948.[5] In the laboratory,[10] evidence is rather strong that a large proportion of heterografts will break down and result in either aneurysms or occlusion of the vessel, but homografts generally do well. We must, however, show some restraint in the use of homografts for conditions that are not potentially fatal or crippling until we know more of their eventual outcome. The same is true of the different types of synthetic materials now being used to replace arteries. Thromboendarterectomy does not carry the threat of incompatible tissue, but has its own threat of later rupture of the vessel or recurrence of occlusion.

In this patient, the obvious threat to the viability of all or part of the left leg was great. We felt justified, therefore, in taking the risk that was associated with the resection of the terminal aorta, common iliacs, and small portions of both of the internal and external iliac arteries and the substitution of an arterial homograft. The later risk of popliteal embolectomy was small, and fortunately this combination of procedures resulted in the complete restoration of the circulation to both legs.

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DOUBLE AORTIC ARCH

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IN THE past ten years rapid strides have been made in surgical correction of certain congenital defects of the heart and great vessels. Among these advances one must include surgical division of a "vascular ring" due to a double aortic arch.

This feat was first accomplished by Robert Gross[1] in 1945. He divided the anterior aortic arch in a 4-month-old baby with symptoms of tracheal obstruction.

Since that time there have been numerous cases reported. In December, 1951, Storey and Crittenden[2] reported one case. In a survey of the literature they were able to find a total of fifty-two cases. Since that time an additional twenty-nine cases have been reported.[3-8]

Although the operative technique necessary to divide a vascular ring is at times not difficult, the postoperative mortality and morbidity are high.

Gross[9] reported a mortality rate of 24 per cent in twenty-one patients, and in the series reported by Riker,[8] the mortality rate was 27 per cent in eighteen patients. Postoperative respiratory obstruction is the most common complication. Tracheotomy is often necessary. Adequate surgical dissection is required to free the encircling "ring" from the trachea and esophagus. The resulting trauma to the trachea may cause sufficient swelling of the mucous membrane to occlude the trachea completely during the early postoperative period.

The purpose of this report is to describe an unusual case of double aortic arch, its surgical aspects, and method of management of the postoperative complications.

CASE REPORT

W. T., a 3-month-old white boy, weighing 11 pounds, 12 ounces, was admitted to St. Francis Hospital on Dec. 6, 1951. The mother stated that the infant had had noisy "crowing" respirations since birth. He had had intermittent periods of "gasping for breath." At the age of 6 weeks, while feeding at the breast, he choked and became very cyanotic. This happened several times. During the two weeks prior to admission he had difficulty in swallowing cereal. Otherwise, the baby had been in good health.

On Dec. 7, 1951, an esophagram was made, using Lipiodol (Fig. 1). The typical posterior "cookie-bite" indentation of the esophagus was seen in the lateral chest roentgenogram. Laboratory examinations were normal, except for a red blood count of 2,890,000, and hemoglobin of 9 Gm. A transfusion of 125 c.c. of whole blood was given on Dec. 10, 1951.

Received for publication March 17, 1955.

A left thoracotomy was performed* on Dec. 13, 1951. Endotracheal anesthesia using cyclopropane was administered.† Using an anterior approach, the chest was opened through the third anterior intercostal space. The second, third, and fourth costal cartilages were divided. The thymus was dissected free and removed from the underlying heart and great vessels. The anterior arch of the aorta and its main branches were all of normal size and in normal position. The left superior mediastinum was then opened. The phrenic and vagus nerves were retracted. A piece of umbilical tape was placed around the left subclavian artery for traction.

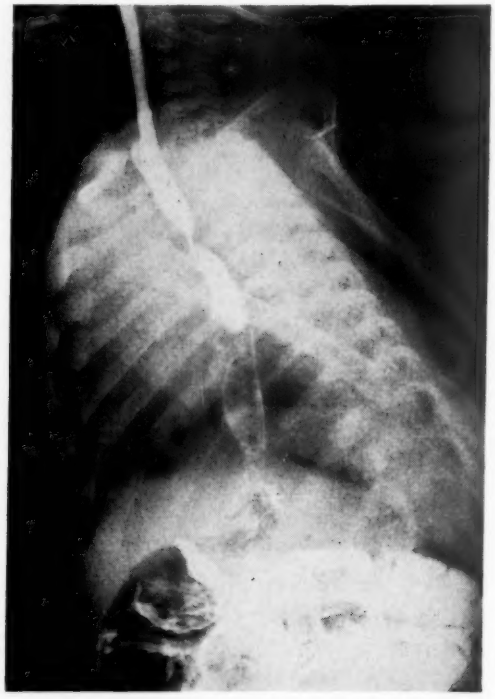

Fig. 1.—Lateral esophagram with Lipiodol showing posterior "cookie-bite" indentation due to double aortic arch.

Further dissection revealed a small posterior arch arising from the ascending aorta and entering the descending aorta distal and medial to the origin of the left subclavian artery (Fig. 2).

Considerable traction on the left subclavian artery was necessary so that sufficient length of the posterior arch could be dissected free for division. During this part of the operation, the anesthesiologist had difficulty in maintaining oxygen exchange. Ligatures of 0 black silk were placed around the posterior arch. It was hurriedly ligated proximally and distally and divided (Fig. 3). After division, the distal end retracted out of sight in the right side of the mediastinum. Oxygen exchange could now easily be performed by the anesthesiologist. The trachea was then dissected free from all surrounding fibrous tissue.

The chest was then closed by approximating the costal cartilages with interrupted 00 chromic catgut. A No. 14 de Pezzer catheter was inserted through the fourth intercostal space for drainage and connected to a water-seal bottle. Three pericostal sutures of 00 chromic catgut were placed around the third and fourth ribs. The muscles of the chest wall were approximated with continuous 00 chromic catgut and the skin with con-

*By Dr. R. A. De Bord.
†By Dr. John Burdon.

tinuous 0000 black silk. The infant received 125 c.c. of blood during surgery and left the operating room in good condition. The total operating time was one hour and fifty minutes.

About six hours following surgery, the baby began to show signs of severe respiratory obstruction with a loud inspiratory stridor, marked suprasternal retraction, and cyanosis. Tracheotomy was performed* approximately eight hours postoperative. It was felt that the obstruction was in the trachea at the site of the constricting ring. Therefore, a low tracheotomy was performed with insertion of a long 00 tracheotomy tube in an effort to pass the tube through the constricted tracheal segment (Fig. 4).

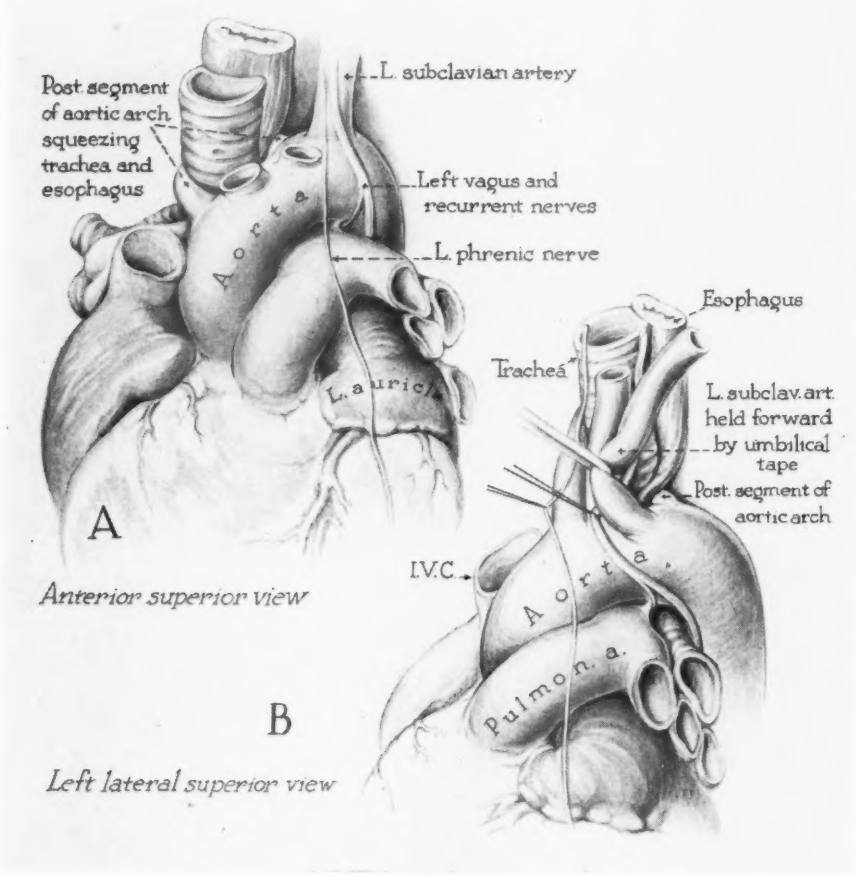

Fig. 2.—Diagram of double aortic arch as seen at surgery.

Following this procedure the baby's condition was much improved. He was placed in a humidified oxygen tent. On the second postoperative day the infant had a short period of respiratory obstruction and cyanosis. This responded to tracheal suction and artificial respiration. A chest roentgenogram revealed atelectasis of the left lung with elevation of the left diaphragm. The chest drainage catheter did not function well and was removed in forty-eight hours.

The skin sutures were removed on the seventh day, at which time the incision was well healed.

*By Dr. Morris H. Cohen.

During the next three weeks the infant had occasional periods of respiratory obstruction and cyanosis. He ran an intermittent fever of 100° F. to 101° F. There was difficulty in maintaining nutrition. He would vomit most of his feedings one day and then retain all feedings the next day.

Gradually, the fever subsided and the feedings were regurgitated only occasionally. The parents were instructed in the care of the tracheotomy tube, and the infant was discharged to his home on Jan. 11, 1952, approximately one month following surgery (Fig. 5).

He was readmitted on Jan. 20, 1952, because of fever and vomiting. Chest roentgenogram again revealed partial atelectasis of the left lung. Bronchoscopy was performed* on Jan. 21, 1952. The left vocal cord did not move. The 3.5 mm. bronchoscope

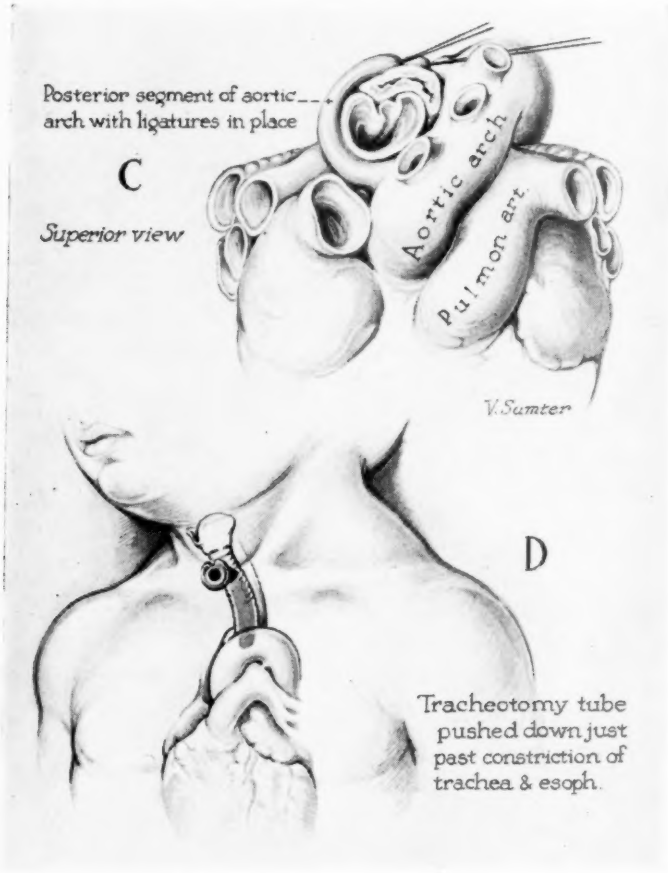

Fig. 3.—Upper diagram showing ligatures in place prior to division of posterior arch. Lower diagram illustrates tracheotomy tube passed through constricted segment.

was inserted through the laryngoscope. The left main bronchus had no visible lumen and appeared collapsed. However, it could be dilated with the tip of the bronchoscope and remained open for a short interval. Fluoroscopy of the chest revealed paralysis of the left diaphragm. Evidently, traction on the vagus and phrenic nerves during surgery was sufficient to cause paralysis of the left vocal cord and diaphragm.

With antibiotic therapy, he again improved and was discharged on Jan. 30, 1952. The third admission was on Feb. 1, 1952, with a fever of 101° F., findings of left bronchopneumonia and vomiting. Because of financial reasons the infant was transferred to the Children's Memorial Hospital in Chicago, Illinois.†

*By Dr. Morris H. Cohen.
†On the service of Dr. Paul Holinger.

During the baby's stay at the Children's Memorial Hospital he had intermittent periods of pneumonitis and fever. He was kept continuously in a steam room and was given varius antibiotics. His condition gradually improved. He was bronchoscoped on six occasions. In March, 1952, it was necessary to cauterize some granulation tissue at the tip of the tracheotomy tube.

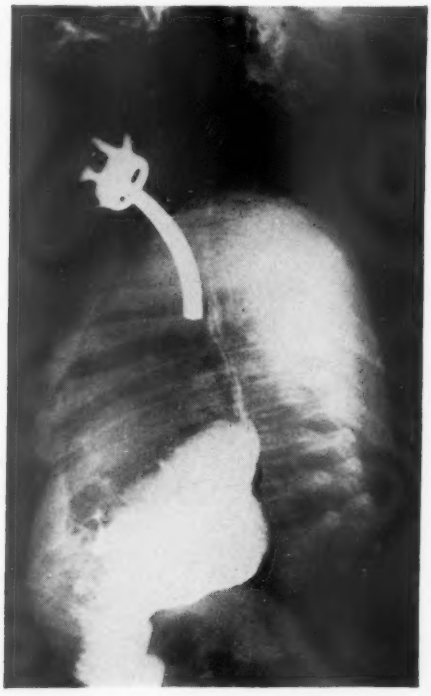

Fig. 4.—Lateral esophagram showing tracheotomy tube in proper position.

Fig. 5.—Photograph of patient at age 4 months showing postoperative incision and tracheotomy.

In May, 1952, the baby tolerated partial plugging of the tracheotomy tube. On June 2, 1952, the tracheotomy tube was removed without difficulty. He was discharged from the hospital on June 3, 1952, weighing 14 pounds, 7 ounces. The last bronchoscopic examination on June 1, 1953, revealed only slight narrowing of the trachea. Both vocal cords moved normally. Subsequent fluoroscopic examination has revealed return of full motion of the left diaphragm. The child has developed normally, has no symptoms, and leads a normal, active life (Fig. 6).

DISCUSSION

A double arch occurs when both the right and left dorsal segments of the fourth aortic arch persist. The embryology involved in the various types of "vascular rings" has been clearly presented by Riker.[8]

Fig. 6.—Photograph of patient at age 2 years showing normal development.

The symptoms of a tight "ring" occur shortly after birth. Noisy "crowing" respirations with both an inspiratory and expiratory stridor are a prominent feature. There may be a brassy cough with repeated respiratory infections.

Dysphagia occurs at the age of 2 to 3 months, with the addition of cereal to the diet. The additional constriction of the trachea while swallowing a bolus of food may be sufficient to cause "choking spells" during feeding.

Although one may suspect the diagnosis from the symptom, the exact diagnosis is made by x-ray examination of the esophagus, using either Lipiodol or barium. The posterior indentation noted in the lateral roentgenogram is diagnostic. The lateral indentation seen in the posteroanterior roentgenogram may give some clue as to a right or left arch.

Surgical division of one of the components of the encircling ring is the only satisfactory method of treatment. Surgery should be performed as soon as the diagnosis is made; otherwise repeated respiratory infections and poor nutrition may make the operation hazardous.

The choice of an anterior or lateral approach is always a problem to the surgeon. There is no doubt that the anterior approach gives much better exposure to the aortic arch and its tributaries. However, if the posterior arch happens to be the smaller, excessive dissection and traction are necessary to allow safe division of the posterior arch. There is no doubt that the postoperative paralysis of the left vocal cord and diaphragm in this case was the result of traction sutures around the phrenic and vagus nerves, even though only light tension was applied to them. This also contributed to the period of severe respiratory obstruction occurring postoperatively, requiring tracheotomy.

Fortunately, we were able to perform an elective tracheotomy in the operating room under good conditions. A long 00 tube was inserted in an effort to pass the constricted trachea (Fig. 4). The care required for a tracheotomy in an infant would compile a chapter in itself. Constant nursing attention is necessary to aspirate secretions and keep the inner tube clean at all times. A small, thick plug of mucus may completely block the airway and cause sudden death.

Irritation of the tracheotomy tube against the esophagus may cause vomiting and it may be difficult to maintain nutrition in a small infant. Certain types of formulas seem to cause excessive bronchial secretion during feeding. It is usually necessary to keep the infant in a humidified oxygen tent, or steam room, for long periods of time.

Because the tracheal rings in an infant are so pliable it is often impossible to extubate the infant until 6 months of age. By then the trachea is of sufficient size and rigidity to prevent collapse once the tracheotomy tube is removed. Of course, intermittent partial plugging of the tube must be well tolerated before it is finally removed.

One of the critical aspects in the handling of such a case is maintenance of proper anesthesia. The encircling arch may be so tight that the anesthesiologist cannot pass an endotracheal tube through the narrowed segment. It may be necessary to give oxygen via a small polyethylene tube passed through the endotracheal tube and beyond the constriction.

It is always disconcerting to the surgeon to find a normally appearing aortic arch and tributaries. However, further dissection may reveal a small,

short posterior arch buried within the mediastinum. To find this vessel it may be necessary for the surgeon to mobilize the aortic arch by division of the superior intercostal arteries.[4] After the arch has been divided, the surgeon should expose the trachea and divide any fibrous strands which might cause continued constriction of the trachea. Division of the ligamentum arteriosum may be of value if there is a small anterior arch.

In each case the infant must be watched closely and elective tracheotomy performed if signs of respiratory obstruction should develop.

SUMMARY

1. An unusual case of double aortic arch is reported.
2. The operative and postoperative complications are discussed.
3. Operation resulted in a normal patient.

We wish to express our appreciation to Dr. Paul Holinger and Dr. Kenneth Johnson for their help during the postoperative period.

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FALSE ANEURYSM OF AORTA FOLLOWING INSERTION OF A PLASTIC VALVE FOR AORTIC INSUFFICIENCY

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AN OPERATIVE procedure for the correction of aortic insufficiency has recently been reported by Hufnagel and his associates.[1] The authors have presented their clinical experience with a plastic ball-type valve inserted into the descending aorta just distal to the subclavian artery in a series of twenty-three patients. The jacket of the valve is made of methyl methacrylate, and the ball may be either methacrylate or polyethylene. Fixation of the valve in the aorta is accomplished by two multiple-toothed circumferential nylon rings. The intermittent circumferential pressure exerted upon the aorta by this ring does not produce aortic necrosis and rupture. The valve is so constructed that a differential pressure of 5 mm. Hg is adequate to open or close the valve. It is estimated by Hufnagel and co-workers that approximately 75 per cent of aortic reflux is controlled by the valve. For additional details regarding the construction and insertion of this valve, the reader is referred to the article by Hufnagel and associates[1] (Fig. 1). The present report deals with the formation of a false aneurysm around a plastic valve of the type described.

CASE REPORT

F. C., a 42-year-old Puerto Rican man, was admitted to the Fourth Medical Service, Bellevue Hospital, on April 6, 1954. The patient stated that he had noted increasing fatigue and dyspnea for two and one-half months prior to admission. Associated with these symptoms there was a sensation of "music in the chest" noted when the patient was lying on the left side. This occasionally served to awaken him from sleep. Additional symptoms reported included episodes of transitory dizziness, paroxysmal dyspnea, profuse diaphoresis, and epigastric discomfort. During the course of the present illness there had been a 25-pound weight loss. The past history was significant in that the patient had had a penile lesion at the age of 20 for which he was treated with one injection of salvarsan a week for six weeks.

The pertinent physical findings were limited to the cardiovascular system. The blood pressure in the arms ranged from 125-130/45 and in the legs from 195-210/55-60. The point of maximal impulse was in the sixth intercostal space at the anterior axillary line. There was a palpable diastolic thrill at the base of the heart. Percussion revealed a heart enlarged to the left. Auscultation revealed a high-pitched musical diastolic murmur audible over the whole of the precordium which was also heard posteriorly. There was an additional soft systolic murmur audible at the apex. A capillary pulse was present in the nail beds, and pistol-shot sounds were easily heard over the femoral vessels. There was moderate enlargement of the liver and distention of the jugular veins.

Received for publication March 8, 1955.

Roentgenogram of the chest revealed moderate cardiac enlargement. An electrocardiogram was reported as showing an incomplete right bundle branch block and left ventricular enlargement. Mazzini and Wassermann serologic tests for syphilis were positive. The spinal fluid Wassermann test was negative.

The medical diagnosis was syphilitic aortitis, aortic valvular insufficiency, and possible rupture of an aortic valvular cusp. The patient was felt to be in congestive failure and was digitalized, placed on a salt-free diet, and given mercurial diuretics. He received six million units of procaine penicillin because of the positive serologic tests.

The patient was transferred to the Fourth Surgical Division, and on June 3, 1954, a left thoracotomy was performed through the fifth intercostal space with resection of segments of the fifth and sixth ribs. The aorta was mobilized for a distance of 3.5 inches beginning immediately distal to the origin of the left subclavian artery. Four pairs of intercostal arteries were ligated during the aortic mobilization. The aorta was cross-clamped and a 1-inch segment excised. The smallest sized plastic valve, sterilized in Zephiran and rinsed with heparin solution, was inserted into the distal aorta and the multiple-toothed ring

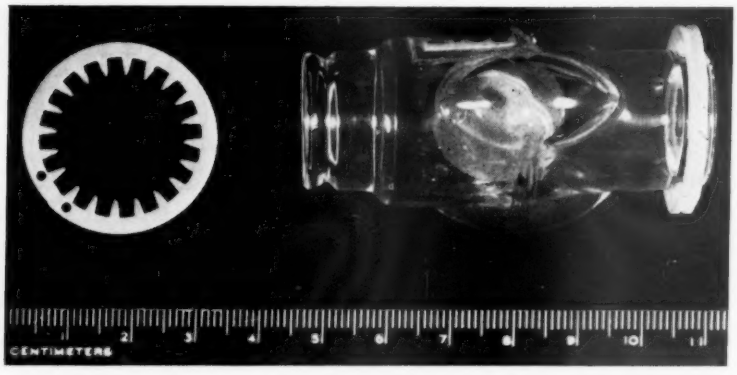
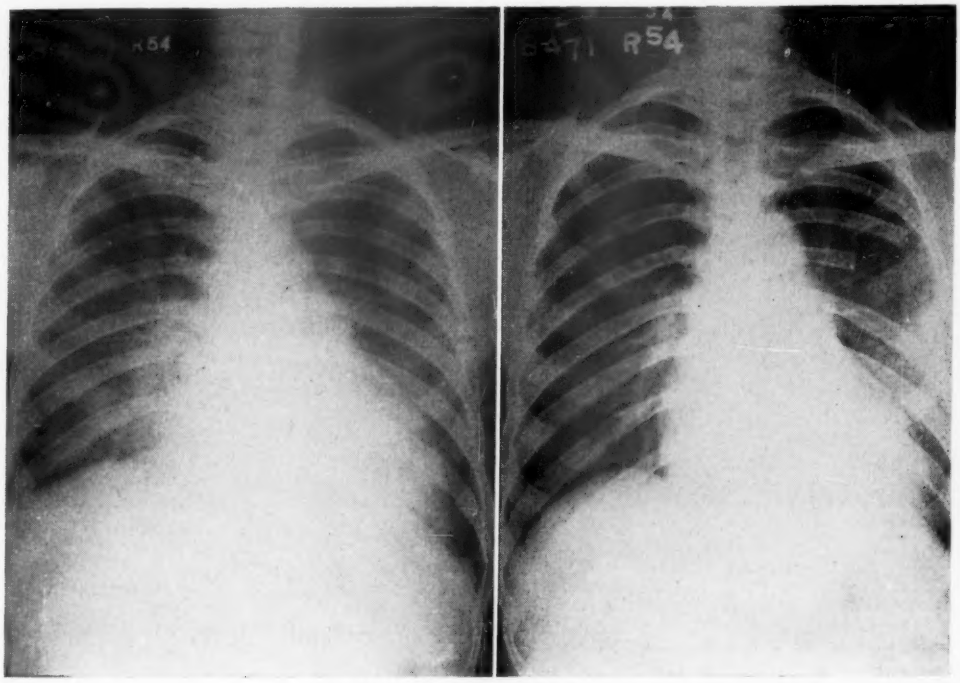


Fig. 1.—Simple ball-type plastic valve similar to valve used in present case presentation.

applied and held in place with a No. 5 braided silk ligature and a No. 30 wire ligature through the appropriate apertures in the ring. There was a slight discrepancy in size between the circumference of the proximal aorta and the valve, so that following application of the multiple-toothed ring, a 1 mm. segment of aortic wall was pinched between the closed edges of the ring. The ring was secured with a No. 5 braided silk ligature and a No. 30 wire suture through the ring apertures. The valve was filled with heparin-Ringer's solution and the distal aortic clamp removed. The patient's head and shoulders were depressed 30 degrees and the proximal aortic clamp removed, following which the blood pressure rapidly fell and heart action became almost imperceptible. The clamp was reapplied and cardiac massage instituted for a period of three to four minutes. Heart action resumed and the blood pressure rose to a systolic level of 100 mm. Hg in the upper extremities. Following a five-minute interval the clamp was again removed with rapid reappearance of hypotension. Reapplication of the clamp resulted in restitution of the blood pressure to 100 to 110 mm. Hg. Following another interval of five minutes, the clamp was gradually removed over a period of three to four minutes without recurrence of hypotension. Therefore, the total time of aortic occlusion was twenty-eight minutes for the insertion of the valve and approximately seventeen minutes of incomplete occlusion utilized for cardiac resuscitation and re-establishment of cardiovascular equilibrium. Valve action was immediately apparent after release of the aortic clamp. The proximal and distal junctions of aorta and valve were wrapped in Gelfoam, a pleural flap sutured over the valve, and the chest closed in anatomic layers following the introduction of a chest tube which was attached to a sterile underwater seal. The excised segment of aorta was reported as showing syphilitic aortitis.

The immediate postoperative course was essentially uncomplicated. The congestive heart failure, present since admission, was treated with Digoxin and mercurial diuretics. For the first four postoperative days, the clotting time was maintained at ten to fifteen minutes by means of aqueous heparin, following which Dicumarol therapy was started, and the prothrombin time maintained at twenty to thirty seconds for a period of three weeks following operation. The congestive failure gradually cleared, and the patient was discharged from the hospital thirty-three days following insertion of the valve (Fig. 2, *A* and *B*).



A. *B.*

Fig. 2.—X-ray films of chest. *A*, Preoperative, *B*, twenty-six days postoperatively. Note diminution in transverse diameter of the heart twenty-six days after insertion of the valve. Actual measurements showed a reduction of 2 cm. in the transverse diameter of the heart.

The patient returned to the hospital on July 15, complaining of severe crushing chest pain in the anterior left chest. The pain radiated to the back and was associated with sweating. There had been a marked increase in the intensity of this pain in the two hours following its onset. The plastic valve action was audible over the entire chest. The blood pressure in the arms was 140-160/20-30 and in the legs it was 145/80. There was no evidence of cardiac failure. Roentgenogram of the chest showed status postthoracotomy and an electrocardiogram did not reveal a myocardial infarction. The patient was sedated and placed in bed. During the following two weeks the episodes of precordial pain, crushing in nature, and radiating to the left posterior chest and the upper abdomen, increased in frequency and duration. On July 28, a chest plate revealed an ovoid mass in the left chest in the vicinity of the plastic valve (Fig. 3). This mass was noted to transmit pulsations on fluoroscopy but intrinsic pulsations were absent. The patient required constant narcotics for relief of chest pain at this time. Repeat chest x-ray examination on August 5 showed an increase in the size of the perivalvular mass and a density in the apex of the left lower lobe (Fig. 4). On August 9, there was hemoptysis of small amounts of bright red blood. The patient became progressively comatose and expired on August 12. Immediately prior to expiration there was a hemoptysis of approximately 300 c.c. of bright red blood.

The salient findings upon post-mortem examination were limited to the left chest. There was a perivalvular false aneurysm containing approximately 200 c.c. of clotted blood. The cuff of aorta beneath the proximal ring appeared to be necrotic throughout the greater part of its circumference. There was a large hematoma between the visceral pleura and

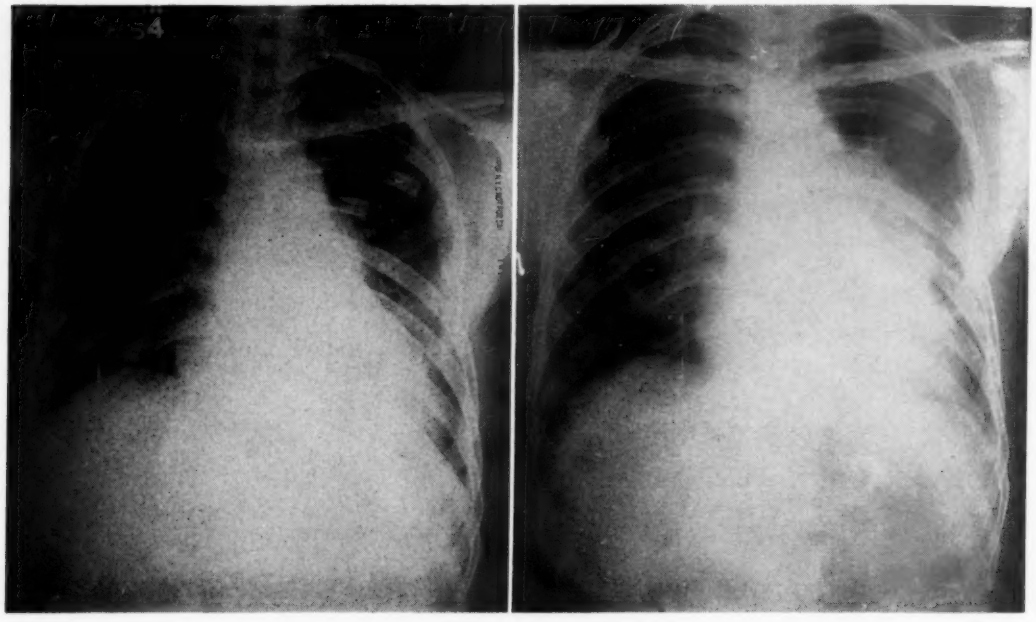


Fig. 3. Fig. 4.

Fig. 3.—X-ray film of the chest forty-one days postoperatively. The perivalvular false aneurysm is seen distal to the aortic arch.

Fig. 4.—X-ray film of the chest taken fifty-four days after operation, illustrating the increase in size of the false aneurysm.

Fig. 5.—The plastic valve is seen surrounded by hematoma and false aneurysm. The clamp is on the distal aorta.

the pulmonary parenchyma of the left lower lobe, and section of this lobe revealed clotted blood in the parenchyma and bronchi of the lobe. No point of perforation could be demonstrated in the left major stem or segmental bronchi. The previously mentioned false aneurysm completely surrounded the plastic valve and was adherent to the posterior chest wall (Fig. 5). Examination of the aortic valve revealed aortic insufficiency which, anatomically, was surprisingly mild. Its clinical significance, however, was attested by the presence of endocardial insufficiency pockets in the outflow tract of the left ventricle. There was no rupture of an aortic valvular cusp to explain the peculiar musical diastolic murmur heard during life. Microscopic examination of longitudinal segments of aorta from beneath the proximal multiple-toothed ring revealed necrosis with an infaretlike pattern (Fig. 6). It

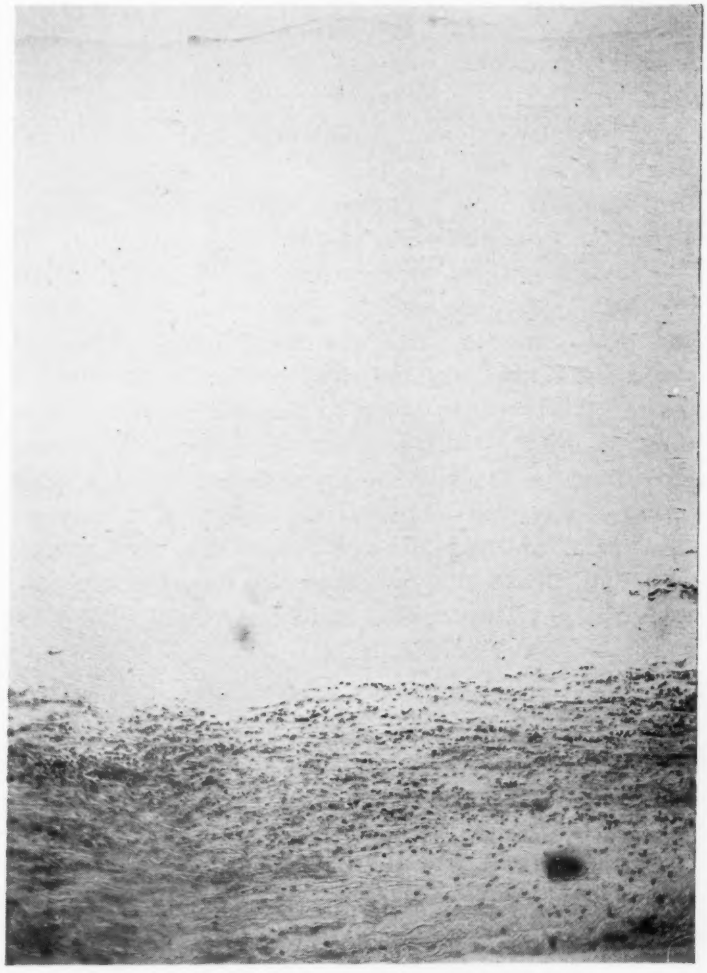


Fig. 6.—Photomicrograph of a segment of aorta beneath the proximal multiple-toothed clamp. Coagulation necrosis of the intima and media is seen. There is a dense infiltrate of polymorphonuclear neutrophils in the adventitia. Two additional microscopic sections from beneath the proximal ring as well as two sections from beneath the distal multiple-toothed ring also showed necrosis. (Hematoxylin and eosin. ×60; reduced ¼.)

was felt that this was the site of bleeding from the proximal aorta. Two longitudinal sections through the aorta beneath the distal ring also revealed necrosis of the media. Microscopic examination of the left lower lobe confirmed the gross findings of hemorrhage in alveoli and bronchi.

DISCUSSION

In view of the technical difficulties associated with insertion of the plastic valve into this patient's aorta, his immediate postoperative course was relatively uncomplicated. X-ray films of the chest approximately three weeks after operation revealed a diminution in the transverse diameter of the heart, presumably the result of diminished dilatation of the left ventricle. Aortic rupture probably occurred shortly prior to the patient's second admission and the acute episode, interpreted initially as a myocardial infarction, resulted from dissection of the visceral pleura of the left lower lobe. After a roentgenogram was obtained, the diagnosis of aortic leak with formation of a false aneurysm was made. However, it was felt that the patient's poor myocardial reserve and his rapidly downhill course contraindicated any heroic measures directed toward the aneurysm.

The source of the perivalvular, subpleural, and parenchymal hematomas of the left lower lobe was found to be an area of aortic necrosis beneath the proximal multiple-toothed ring. Through this necrotic zone, thrombus was continuous between the proximal aorta and the false aneurysm. The etiology of this localized necrosis is subject to speculation. A factor which immediately comes to mind is that of syphilitic aortitis. Microscopic examination of the aortic specimen excised at the time the valve was inserted revealed an active syphilitic aortitis. Although the chronic inflammatory process in the aortic wall may have increased the susceptibility of the aorta to necrosis following local trauma, this would not appear to offer a satisfactory explanation. Approximately 20 per cent of the individuals in Hufnagel's series had syphilitic aortitis, and while marked thickening of the wall increased the difficulty of valvular insertion in one case, eventual aortic necrosis did not occur. We are unaware of any data suggesting that syphilitic aortitis increases the susceptibility of the vessel to necrosis following the application of a suitable vascular clamp or the insertion of sutures.

A further explanation of the aortic necrosis may have been the production of undue tension on the aortic wall at the point of fixation of the proximal multiple-toothed ring, resulting in necrosis of an intervening zone of aortic wall. A 1-inch segment of aorta was excised prior to insertion of the plastic valve. However, no undue tension at the proximal or distal sites of fixation of the aorta to the valve was noted at the time of operation.

Finally, the disparity in circumference between the aorta and the grooved end of the plastic valve necessitated the insertion of one plicating suture in the proximal aorta to obtain satisfactory union between the valve and aorta. The potential necrotizing effect of this suture approximating 1 mm. of anterior aortic wall does not account for the multiple circumferential areas of medial necrosis seen on microscopic section of the proximal aorta. In contrast, the microscopic findings resemble those reported following complete encirclement of the aorta by a constricting band or ligature with subsequent pressure necrosis secondary to interruption of the nutrient vasa vasorum. We conclude that the principle of intermittent circumferential aortic fixation as attempted by a

multiple-toothed ring was unsuccessful in this case and that the ring produced extensive circumferential compression of the vasa vasorum with resultant necrosis of the aorta. A possible solution to this problem would lie in the construction of a valve with a proximal diameter one-eighth inch greater than the distal diameter with appropriate multiple-toothed rings to compensate for the discrepancy in the circumference of the proximal and distal segments.

SUMMARY

An ingenious method for partially reducing aortic reflux in aortic insufficiency has recently been reported.[1] This method utilizes a plastic valve of a simple ball type which is inserted into the descending aorta. A case is reported in which localized necrosis of the aortic wall followed insertion of this valve. A perivalvular false aneurysm, subpleural hematoma, and intrapulmonary hemorrhage with eventual death resulted. The etiology of the aortic necrosis is not certain and has not been experienced by others who have used the principle of multiple-point fixation of the aorta. It is suggested that extensive compression of the aortic vasa vasorum by the multiple-toothed ring was responsible for the diffuse aortic necrosis found on post-mortem examination.

Acknowledgment.—We wish to thank Dr. Norman S. Cooper of the Department of Pathology, Bellevue Hospital, for reviewing the post-mortem findings.

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CARCINOID TUMOR OF TRANSVERSE COLON COMPLICATED BY GASTROCOLIC FISTULA

Survival Following Resection

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CARCINOID tumor of the colon is extremely uncommon and gastric fistula is also rare, but a combination of these two lesions in the same individual is even rarer. In a thorough investigation of the medical literature, we have been unable to find a previous case of gastrocolic fistula resulting from a carcinoid tumor arising in the transverse colon. The following case, which recently came to our attention, is believed to be the first recorded case of this kind. It is of additional interest because it is, as far as we have been able to determine, the seventh reported case of malignant gastrocolic fistula in which the patient survived surgical resection.

CASE REPORT

Mr. V. O., a 60-year-old man, was first seen at the Ochsner Clinic on Aug. 29, 1954. About four months before this, he had been hospitalized elsewhere for ten days because of vomiting after meals and on other occasions, and was treated with antacids and iron. He did not return to work for nine weeks, during which time his condition failed to improved. He could not eat solid foods, vomiting undigested food intermittently throughout this period. The vomitus often looked and smelled like feces and the frequent eructations had the odor of fecal gas. During the four months of his illness, he had lost 74 pounds in weight and had noticed increasing fatigability, weakness, and anorexia. The daily bowel movement frequently contained undigested food. There was no history of diarrhea, hematemesis, or melena, and throughout the course of the illness he had never had any pain.

Palpation of the abdomen disclosed a large, nontender, movable mass approximately 15 cm. in diameter in the left upper quadrant. Manipulation produced mild epigastric discomfort.

Results of hematogram, urinalysis, serology, fecal examination for parasites, and electrocardiography were within normal limits. The sedimentation rate was 61 mm. per hour by the Westergren method.

Roentgenogram of the chest revealed no abnormalities. On fluoroscopic examination the esophagus appeared normal. A fistula was visualized between the greater curvature of the stomach and the transverse colon just proximal to the splenic flexure (Fig. 1). Nearly all the barium meal passed directly into the colon with little emptying into the duodenum. Examination by barium enema revealed a redundant splenic flexure. The fistulous tract was again demonstrated, beginning proximal to the splenic flexure and connecting with the greater curvature of the stomach (Fig. 2). The barium also passed beyond the fistula, revealing that the remainder of the colon was normal.

Five days after admission, the abdomen was explored through an upper transverse abdominal incision under general endotracheal anesthesia. The large, firm, nodular mass between the stomach and transverse colon occupied the greater portion of the transverse mesocolon and overlying adherent omentum. There were no visible or palpable metastatic

Received for publication March 15, 1955.

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nodules within the liver or on other viscera. A biopsy specimen from the anterior aspect of the mass revealed invasive neoplastic disease on microscopic examination by frozen section technique.

The mass and fistulous tract were resected en bloc by subtotal gastrectomy and transverse colectomy with removal of the omentum. The hepatic and splenic flexures of the colon were mobilized and end-to-end anastomosis was performed, the inner layer being of continuous 000 atraumatic chromic catgut and the outer, reinforcing layer of interrupted quilting cotton sutures. Anterior isoperistaltic gastrojejunostomy was then performed with the inner layer of 000 atraumatic chromic catgut and the outer layer of interrupted quilting cotton sutures. Recovery was uneventful and the patient left the hospital greatly improved on the eleventh postoperative day.

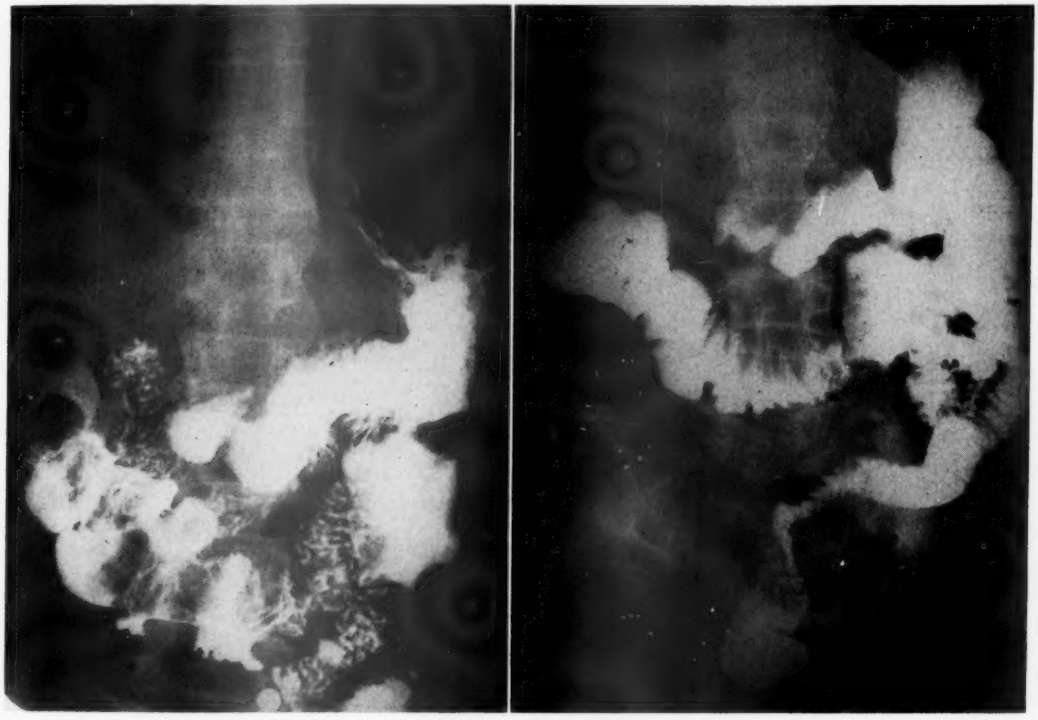

Fig. 1. Fig. 2.

Fig. 1.—Roentgenogram following barium meal demonstrating fistulous tract between greater curvature of stomach and transverse colon.

Fig. 2.—Roentgenogram following barium enema demonstrating fistulous tract between colon and stomach with normal proximal colon.

Grossly, the specimen consisted of a stomach, transverse colon, omentum, and the attached mesentery of the stomach and colon. On the anterior wall and greater curvature of the stomach, 7 cm. from the pylorus, there was a firm, grayish white to yellowish orange indurated mass measuring 7 by 5 by 5 cm., involving the wall of the stomach and extending throughout the gastrocolic ligament to the colon. In the center of the mass was a fistulous tract, one end opening into the stomach, the other into the colon (Fig. 3). The gastric stoma, which measured 2.5 cm., was ovoid, with the mucosal surface beveling over into the fistulous tract. The colonic opening was 4.5 by 3.5 cm. in diameter. An annular constricting mass entirely surrounded by a 5 cm. segment of colon at this point was confluent with the mass on the serosal side that extended to the stomach (Fig. 4). This obstructed at least 60 per cent of the lumen of the colon. Twenty lymph nodes were found in the mesentery of the colon and stomach. The largest node measured 1.6 by 1 by 1 cm.

Microscopically, there were extensive replacement and invasion by a neoplastic growth composed of solid groups and cords of small polyhedral cells, with round vesicular nuclei and pink-staining cytoplasm (Fig. 5). The tumor was growing in typical carcinoid fashion. It invaded the mucosa, submucosa, and muscularis and extended into the subserosa and surround-

Fig. 3.

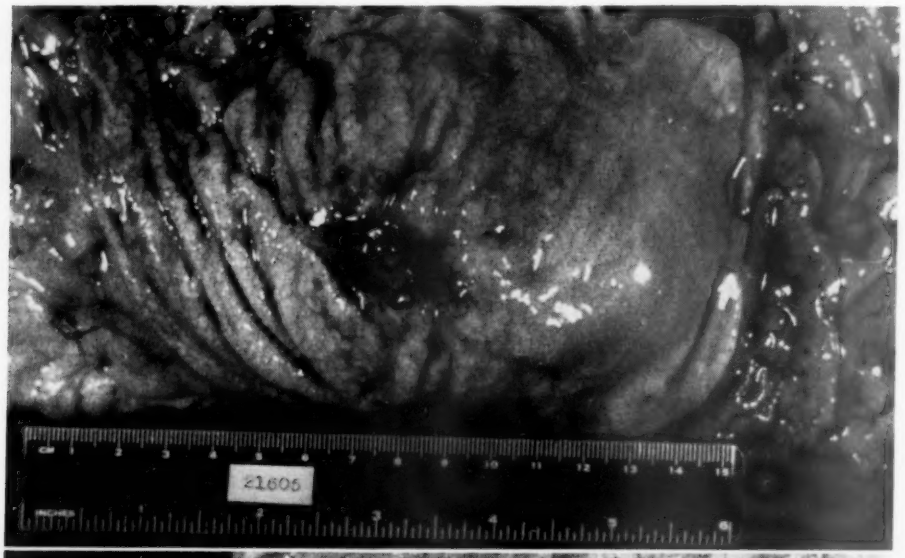

Fig. 4.

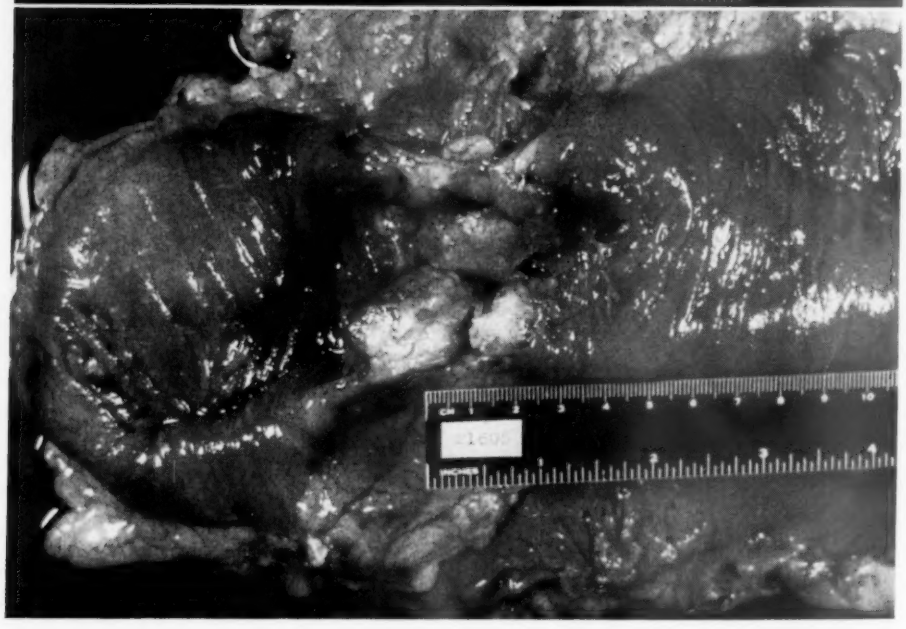

Fig. 3.—Gross specimen of stomach opened along lesser curvature revealing fistulous tract on greater curvature.

Fig. 4.—Constricting lesion of colon with fistulous opening.

ing structures. Sections through all the lymph nodes revealed no evidence of metastasis. The microscopic diagnosis was carcinoid tumor of the transverse colon invading the pericolic tissues and producing a gastrocolic fistula.

Comment.—All carcinoid tumors are potentially malignant. They grow slowly, as a rule, and this undoubtedly was true in the present case. Although the regional lymph nodes were not involved, the tumor was so extensively invasive that the patient cannot be considered cured at this time. He is an ideal candidate for a "second look" with the promise of long survival.

DISCUSSION

Gastrocolic fistula develops more commonly as a complication of carcinoma of the stomach than of the colon. Chavannaz[1] concluded from a review of forty-four cases of gastrocolic fistula secondary to neoplasms that only six were complications of carcinoma of the colon.

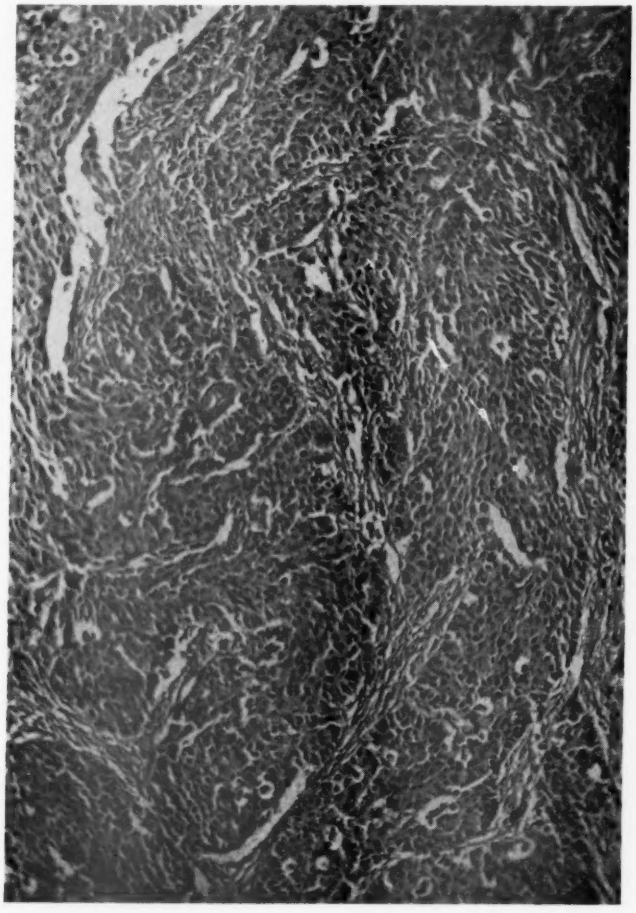

Fig. 5.—Photomicrograph showing solid groups and cords of carcinoid tumor. (×40; reduced ⅓.)

The curative treatment of gastrocolic fistula is surgical resection. This requires radical excision and the operative mortality rate is high. Among 156 cases of gastrocolic fistula secondary to neoplasms of the stomach or colon, collected by Schweitzer and Osburne[2] in an extensive survey of the literature, only six patients survived surgical resection. A single stage operative procedure is preferred, but if the condition of the patient will not permit this, preliminary

cecostomy, colostomy, or ileocolostomy, short-circuiting the fistula, may be done. This will enable the debilitated patient to regain sufficient strength to tolerate resection of the fistula without prohibitive mortality. If the short-circuiting procedure is not performed, main direction of flow in the fistula is from the colon into the stomach, and passage of the colonic content into the small intestine irritates the mucosa of the small intestine, producing hyperperistalsis with rapid development of malnutrition, weight loss, and severe debilitation.

SUMMARY

As far as we have been able to determine, the first case of a gastrocolic fistula due to a carcinoid tumor of the colon and the seventh case of a patient with malignant gastrocolic fistula to survive operation is reported.

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RADIATION STRICTURE OF THE SMALL INTESTINE

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FOR a number of years clinical surgeons have recognized that the intestinal tract is sensitive to the effects of radiation applied to the abdominal cavity or pelvis. Todd,[18] reporting on his experiences in a number of hospitals in England, stated that approximately 5 per cent of the patients receiving pelvic irradiation gave evidence of some degree of intestinal damage. Corscaden[4] reported an incidence of 8.7 per cent intestinal injury for treatment of carcinoma of the cervix by radiation. Other writers[1, 2, 13] have noted complications in the bowel in as high as 16.9 per cent of the patients treated.

Experimental evidence has been presented which indicates that the small intestine is more radiosensitive than either the stomach or the colon,[5, 6, 9, 19] but this interesting fact is not substantiated clinically. The close proximity of the pelvic colon and rectum to the "target" area probably accounts for the fact that 75 to 90 per cent of the intestinal complications to radiation are in the distal portion of the large bowel.

Small intestinal injury, when it occurs, is almost always limited to the terminal four to six feet of ileum and most commonly at the ileocecal junction. The jejunum is involved so rarely that we could find mention of only seven cases in the American literature for the last thirty years, and in each of these cases the jejunal injury was an extension of a process involving a more distal segment of intestinal tract. Massive necrosis, intoxication, and death occurred in the early postradiation period in every instance.

It seems of interest, therefore, to discuss the following case, recently treated at St. Luke's Hospital. This patient proved to have a jejunal stricture approximately six inches from the ligament of Treitz, becoming clinically evident seven years after radiation therapy for carcinoma of the cervix. To the best of our knowledge, this represents the only complication of this type to radiation therapy which has appeared in the American literature.

CASE REPORT

A 68-year-old white woman was admitted to St. Luke's Hospital on May 21, 1954, with the immediate complaint of a severe colicky pain in the mid-epigastrium, accompanied by nausea and vomiting present for forty-eight hours. The pain was well localized and there was no radiation to the shoulders, back, or lower abdominal quadrants. The patient was aware of a rumbling and gurgling in the abdomen during the periods when the pain was at its peak. Her bowels had moved normally the morning of admission and she had been passing gas throughout the day. There had been no fever or chills. The pain had become progressively worse, and at the time of admission to the ward, the patient was crying aloud and thrashing about the bed in distress.

Received for publication March 15, 1955.

Further questioning revealed that similar, less severe episodes had been occurring for a period of approximately two years. Originally, the pain had been mild and had passed away in a matter of two or three hours with only occasional nausea or vomiting. The attacks had increased in frequency and intensity, however, and for the month prior to admission had occurred every five or six days, lasting as long as ten to twelve hours. Vomiting seemed to relieve the pain somewhat, but on several occasions the family physiciain had been called to administer a hypodermic injection. Although the patient had been given a complete gastrointestinal x-ray examination by this physician, no pathology could be found. The patient's family had been advised that her trouble was probably psychosomatic and the possibility of a narcotic addiction had been suggested.

Past history revealed that in 1945 the patient had received a course of x-ray therapy in a small rural hospital for a carcinoma of the uterine cervix. The exact amount of radiation could not be determined because of the death of the attending physician. Four years later she had developed a bladder infection which she was told was due to the effects of the radiation treatment. This infection cleared up in a few months with repeated irrigations of silver nitrate solution, and there had been no recurrence of the difficulty. There was no history of other illness or surgical procedures.

Physical examination revealed a markedly dehydrated white woman in obvious distress, with temperature 99.4° F. orally, pulse 80, blood pressure 140/80. The ears, nose, and throat were negative with the exception of a fetor ex oro and an extremely dry mucous membrane and coated tongue. The chest was clear and the heart tones normal. Examination of the abdomen yielded no evidence of peritoneal irritation, distention, or palpable masses. There was some tenderness to deep palpation in the epigastric region. Loud peristaltic rushes were heard in the same region during the bouts of colic. Rectal examination revealed normal sphincter tone, soft feces in the rectal ampulla, and no masses felt. There was no blood on the examining finger. Pelvic examination was negative. Neurological examination was entirely normal. A scout roentgenogram of the abdomen was negative.

Examination revealed red blood count 3,540,000; white blood count 3,800; hematocrit 33 per cent; differential lymphocytes 22, monocytes 2, basophils 1, neutrophils 69, bands 6; urinalysis: pH 6.0 specific gravity 1.000; sugar one plus, albumin negative, microscopic negative; nonprotein nitrogen 26 mg. per cent; chlorides 108 meq. per liter; sodium 146.2 meq. per liter; potassium 5.57 meq. per liter; total proteins 5.17 Gm. with 2.65 Gm. of albumin and 2.52 Gm. of globulin; sedimentation rate 13 mm. per hour; Veneral Disease Research Laboratory serology negative for syphilis.

Hospital Course.—The patient was given morphine grain 1/6 every six hours and intravenous fluids were administered. The following day the patient was free of pain and the physical examination was still essentially normal. Because of the absence of distention, a tube was not placed into the stomach or small intestine but the intravenous fluids were continued for three more days. The patient remained free of pain and nausea during this time and there was a normal temperature during the entire period. The patient began taking liquids by mouth with no distress. A gall bladder visualization and x-ray study of the stomach and small intestine were undertaken which revealed a normally functioning gall bladder and no evidence of pathology in the stomach, duodenum, or small intestine. The barium passed into the descending colon and rectum in normal time with no evidence of obstruction noted. Repeated blood counts and chemistries during the hospital stay were normal.

On May 28, 1954, the patient was taken to the operating room and given a general anesthetic. The abdomen was opened through a right upper paramedian incision and exploration was carried out. The abdominal and pelvic cavities and their viscera were entirely normal with the exception of a segment of jejunum starting approximately six inches from the ligament of Treitz, which was found to be somewhat edematous and thickened, although it was lying free of adhesions. In three separate areas in this segment, approximately two inches apart, the jejunum was strictured by firm, white scar tissue covered with telangiectasia. The mesentery was somewhat thickened but was normal otherwise. It was difficult to force the intestinal contents manually through this area in the bowel, and manipulation caused a

moderate amount of bleeding from the contracted and injected serosal surface at the sites of stricture. The entire segment of jejunum was resected with approximately two inches of normal intestine both proximal and distal to the area, thus removing eighteen inches of small bowel. An end-to-end open anastomosis was carried out and the abdomen was closed without drainage. The patient made an uneventful recovery and left the hospital on the eleventh postoperative day. The patient has been followed in the office since her hospitalization and at the present time, nine months since her operation, she is without symptoms, has gained weight and is again working.

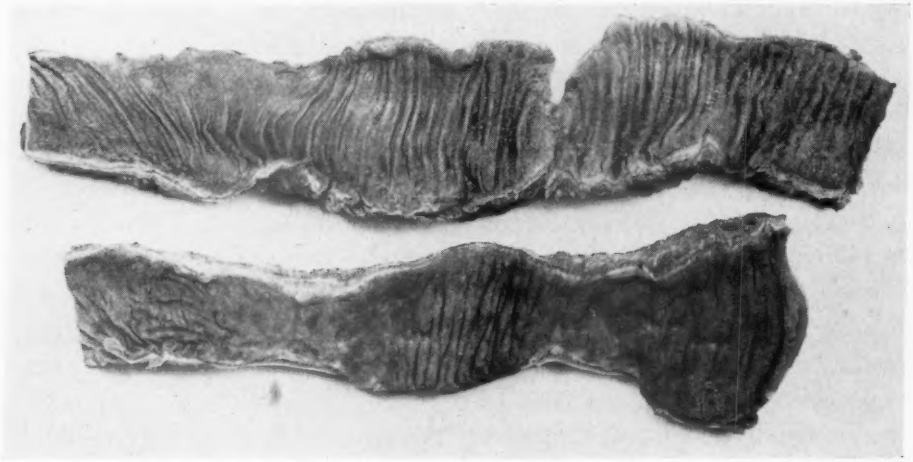

Fig. 1.—The surgical specimen has been opened lengthwise to show better the degree of stricture. This segment of jejunum began at approximately six inches from the ligament of Treitz.

Gross examination revealed a 40 cm. segment of jejunum containing three areas of stricture (Fig. 1). The lumen of the bowel had been narrowed to 5 mm. in diameter at the most proximal stricture. The mucosa was thick and granular and had lost its usual circular folds. The wall of the bowel at the point of the strictures was dense and inflexible. Microscopic examination revealed nonspecific inflammatory reaction with edema, infiltration of lymphocytes, plasma cells, and polynuclear leukocytes, many with eosinophil granules. There is dense hyalinization of the blood vessels and a considerable amount of fibrillar fibrous tissue. The pathologic diagnosis was multiple radiation scar tissue strictures of the small bowel.

DISCUSSION

The pathogenesis of radiation injury to the small intestine follows a well-defined pattern.[5, 9, 19] An initial epithelial reaction of edema and hyperemia gives symptoms of nausea, vomiting, and cramping with occasional diarrhea during, and for a few days or weeks following, the administration of the radiation. More severe early reaction may occur, in which the initial process progresses on to ulceration, necrosis, infection, and hemorrhage,[5, 14] and the patient suffers the so-called radiation intoxication with ultimate death in the early postradiation period.

The primary reaction, however, may be followed by regeneration of the tissue with eventual residua in the areas affected. Hyalinization and scarring are probably the most common residue, but granulation, ulceration of the mucosa, and telangiectasia may also occur. Any of these late manifestations may eventually lead to clinical symptoms of obstruction, hemorrhage, perforation, or

fistula formation.[3, 4, 10] It is unusual for these symptoms to appear more than two or three years after treatment although Frank and Pohle's case[8] went eight years, and the present one seven years, before symptoms became evident. The longest elapsed period is reported by Gardner and Anlyan,[10] whose patient consulted them twelve and one-half years after therapy had been given.

Radiation stricture of the small bowel is an interesting and important problem to the clinical surgeon. The increasing popularity of postoperative radiation therapy for abdominal or genitourinary malignancy, for retroperitoneal tumors, and for pelvic or menopausal abnormalities will undoubtedly lead to more patients in whom the intestinal tract is affected. Diagnosis of the lesion may be a difficult task, for barium studies will not aid in locating the involved segment of small bowel unless almost complete obstruction is present. Laboratory analysis does not always reflect the seriousness of the disease as measured by the patient's complaints of pain, nausea, and intermittent diarrhea. When obstruction occurs high in the jejunum, as was seen in our case, physical signs cannot be relied upon to substantiate the diagnosis.

One is hesitant, naturally, to re-explore a patient who gives a history of malignancy and who returns with complaints which could indicate an extension of the process. Then, too, the label of psychoneurosis offers a pitfall which may prolong or deter the correct diagnosis. Awareness of the possibility that stricture can occur months or even years after the bowel has been exposed to radiation must, therefore, be considered an important aspect in the diagnosis of this lesion. Although recognition is difficult, adequate surgical correction, either by resection or sidetracking of the strictured segment, offers every opportunity for recovery and rehabilitation.

SUMMARY

A case of radiation stricture of the proximal jejunum manifest seven years after therapy is presented. This area of the small intestine is very rarely injured as a result of pelvic radiation, and as far as we can determine this is the first complication to the intestinal tract of this type to be reported. Surgical resection of the lesion has removed all symptoms and the patient is in good health nine months after operation.

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CONGENITAL BIFID STERNUM

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CLEFT sternum with ectopia cordis is a relatively infrequent anomaly. Until 1947, there were no reported surgical corrections of this defect during infancy. It was at this time that Burton[1] reported two cases of repair of nonfusion of the greater portion of the sternum, one case of which was in an infant

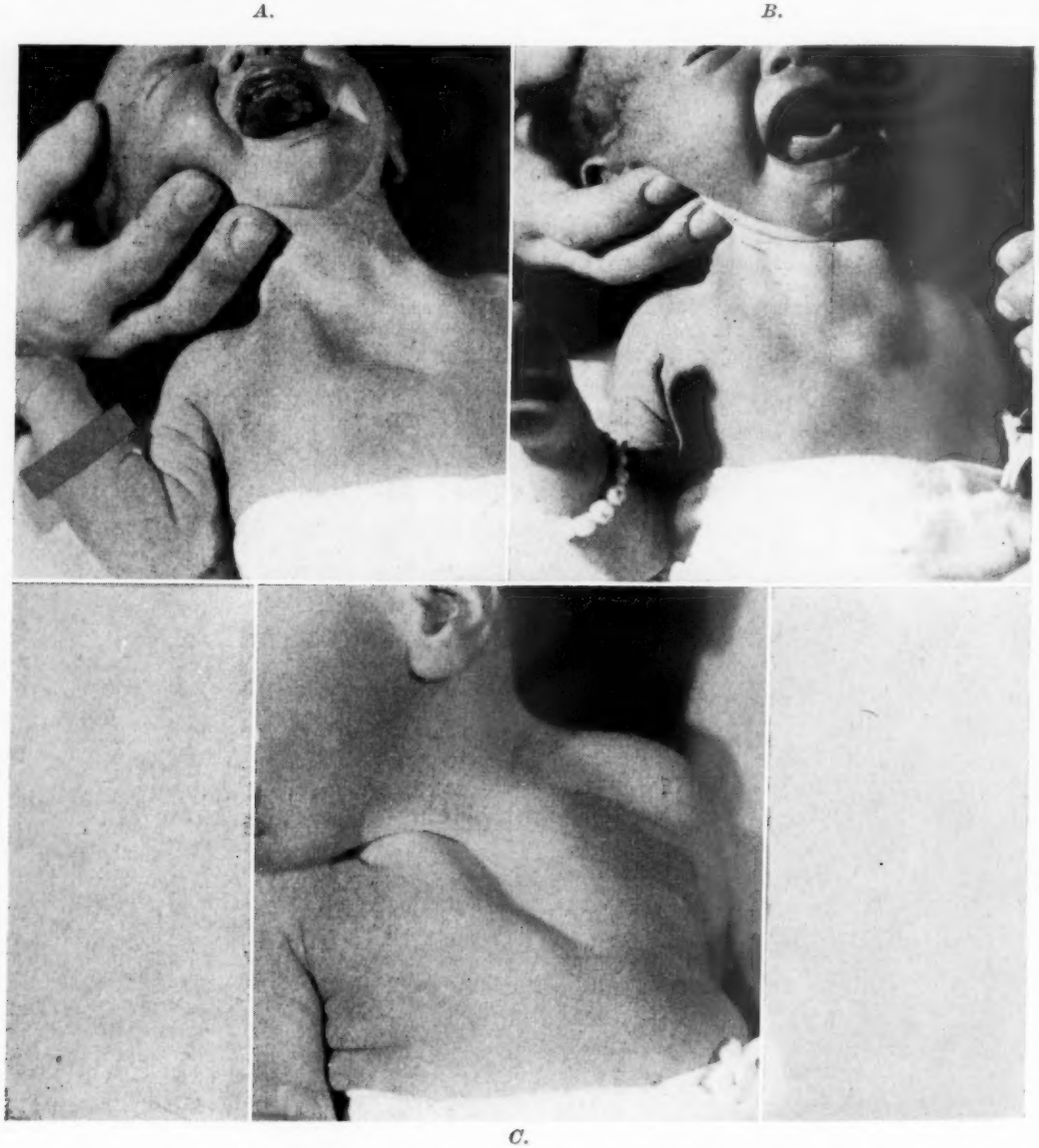
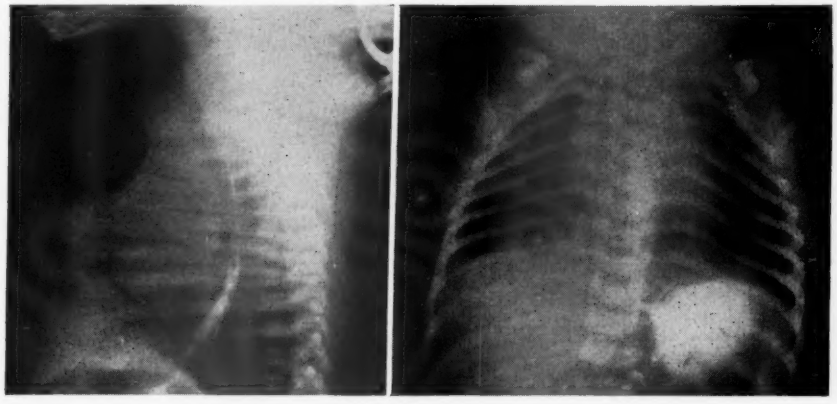


Fig. 1.—Preoperative photographs showing sternal defect. *A*, During inspiration and crying; *B*, during expiration and crying; and *C*, during inspiration at rest.

Received for publication Jan. 30, 1955.

and the other in a 12-year-old child. Then, in 1949, Maier[2] reported on his experience in the correction of a complete sternal separation in a 6-week-old infant with a successful outcome. In a discussion of Maier's paper, Klassen[3] reported a case of cleft sternum with partial ectopia cordis repaired by him in 1948. Since that time there have been no further cases in the American literature on the surgical aspects of this subject. It consequently seemed worth while to us to report the following case of sternal malformation and partial ectopia cordis with a successful surgical repair.



A. *B.*

Fig. 2.—*A*, Lateral film of chest showing sternal defect on inspiration; *B*, posteroanterior film of chest showing wide mediastinum and marked separation of medial end of clavicles.

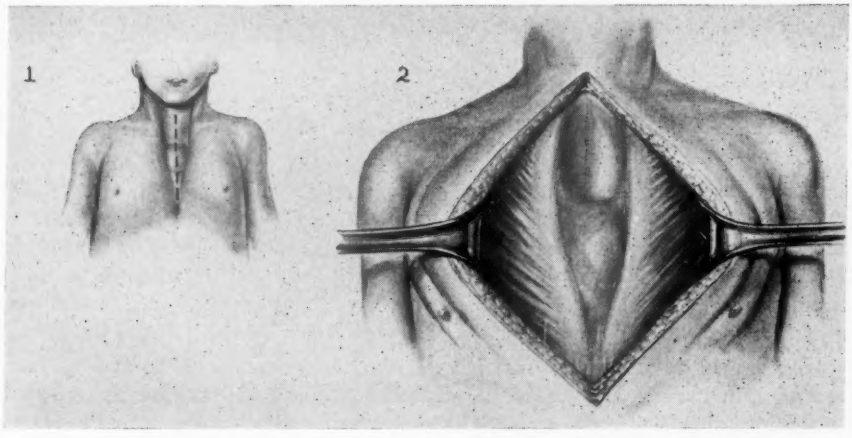


Fig. 3.—Sketch of operative exposure of sternal defect.

CASE REPORT

R. B., a male infant, was admitted to The Children's Medical Center on Aug. 23, 1952, four hours after birth, because of moderate dyspnea and bulging in the sternal area. Pertinent history revealed that the child was the product of a first pregnancy which terminated three weeks prematurely. The prenatal course had been entirely uneventful with the mother suffering from no known infectious episodes or vaginal bleeding. The family history revealed no previous congenital abnormalities.

On physical examination the child appeared to be a well-developed, well-nourished male infant, weighing 5 pounds, 2 ounces, with only slight respiratory embarrassment while in oxygen. There was no cyanosis noted. The only positive physical finding was a defect in the sternum starting at its most cephalad portion and extending caudally to the ziphoid process (Fig. 1). Over this area there was marked paradoxical motion on respiration, and on closer examination the cardiac impulse could be seen through this defect. When the child cried the thoracic viscera could be seen to bulge through the sternal defect. The lungs were clear to auscultation.

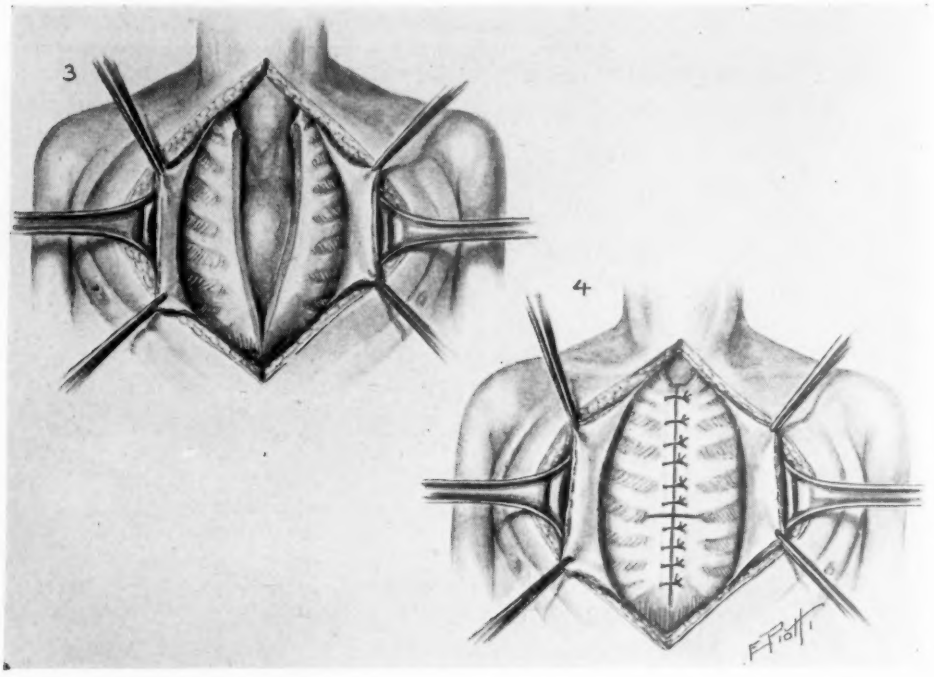


Fig. 4.—Sketch of operative repair of sternal defect.

Laboratory findings revealed a hemoglobin of 20.0 Gm., red blood count of 6.0 million, and a white blood count of 14.8 thousand with a normal differential. Urinalysis was not remarkable. Fluoroscopic and x-ray examination of the chest showed the lungs to aerate and deaerate equally and well with moderate retraction of the anterior chest wall between the bifid sternum. This was most noticeable during forced inspiration. There was definite widening of the space between the anterior ends of the clavicles (Fig. 2).

On Aug. 29, 1952, at the age of 6 days, the child was taken to the operating room, where the defect in the sternum was repaired. Cyclopropane anaesthesia was given by closed system. A longitudinal incision was utilized starting at the base of the neck and going down to the xiphoid cartilage. The subcutaneous tissue was incised until the pericardium was exposed, and was then dissected laterally until the pectoral fascia was encountered (Fig. 3). The pectoral fascia along with the pectoralis major muscle and fascia were obtained for closure of the defect. By blunt resection the pericardium and pleura were dissected free from the posterior surface of the sternal bands. In the hope of obtaining firm union of the sternal bands their rounded edges were removed. The xiphoid process, which was not involved in the cleft, was divided at the midline. The sternal bands were then united at the midline using interrupted 00 silk sutures. In closing the upper portion of the sternum, the lower portion was seen to override; therefore, an incision was made across both sternal bands at the fifth intercostal space and in this way the overriding was eliminated (Fig. 4). The

pectoral fascia was united over the closed sternum with interrupted silk sutures. The subcutaneous tissues and skin were then closed with the same material. A drain was left beneath the pectoral fascia for the evacuation of any fluid accumulation.

Postoperatively, the child was kept in an Isolette with oxygen and Mistogen for seven days, receiving penicillin and streptomycin parenterally. The entire period was uneventful except for an extremely rapid respiratory rate of 80 to 90 per minute, which gradually decreased over the following eight days. Mucous accumulation was of no significance as the baby appeared to be able to handle this much more successfully than preoperatively. The

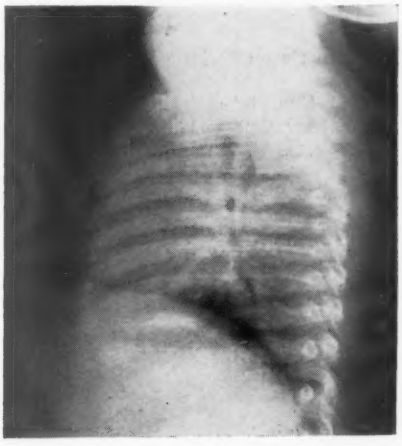


Fig. 5.—Lateral postoperative view of chest showing normal sternal contour without evidence of calcification, taken thirteen months after surgery.

Fig. 6.—Photograph of patient thirteen months postoperatively showing normal chest contour.

drain in the subpectoral space was removed on the fourth postoperative day and the sutures on the eighth, at which time the wound appeared well healed with no evident defect remaining in the sternum. The patient was discharged on the tenth postoperative day.

Since leaving the hospital the child has been completely asymptomatic and there has been no evidence of recurrence of the sternal defect. When last seen, at the age of 13 months, x-ray examination revealed a sternum of normal contour without any evidence of ossification (Fig. 5). Physical examination at this same time also showed a solid anterior chest wall in the area of the previous sternal defect (Fig. 6).

It is our belief that infants born with sternal defects such as this child's should undergo surgery as soon as the general physical condition warrants. The reasons for this are twofold. First, Maier has shown that with the growth of the child, the defect becomes progressively larger and consequently presents increasingly difficult technical problems in its repair. Second, because of the respiratory difficulties caused by the paradoxical motion of the thoracic viscera through the defect, early closure is of paramount importance, and as was shown in our case actually improves respiratory physiology.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

CARDIAC ARREST: FURTHER STUDIES ON THE EFFECT OF pH CHANGES ON VAGAL INHIBITION OF THE HEART*

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INTRODUCTION

IMPENDING death under anesthesia is a subject of cardinal importance to every surgeon. Experience has taught me that cardiac arrest can occur in any patient, with any anesthetic agent and with any anesthetist. For obvious reasons a general emergency surgeon must expect to hear the beating of the wings of the angel of death more often than do surgeons engaged in special branches of our art. Even so, let him who thinketh he standeth take heed lest he fall from unpreparedness. To prick the ventricle within three-quarters of a minute of ascertaining that the heart has ceased to beat, and in the likely event of this single procedure being ineffective, forthwith to massage the heart, will, I am sure, recall some of those whom Charon had started to ferry across the waters of the Styx''—Hamilton Bailey (1947).

In the years following Bailey's rather florid statement of the problem, the awareness and/or incidence of cardiac arrest has increased to such an extent that reports of successful cardiac resuscitation are rather commonplace throughout the world literature.

However, more efforts have been directed toward early diagnosis and immediate treatment of this condition than toward its genesis and prophylaxis. Most clinicians are aware of the importance of adequate blood oxygenation, but the dangers of carbon dioxide accumulation in the blood, even in the presence of normal blood oxygenation, have been neglected somewhat until recently. Evidence for the occurrence of respiratory acidosis during surgical procedures is well documented. Vagal and/or vagovagal reflexes have been indicted clinically as causing cardiac arrest. It seemed important to investigate the effects of controlled vagal stimulation in the intact animal under conditions of altered blood pH in order to confirm or deny clinical impressions.

REVIEW OF THE LITERATURE

For as long as surgery has been practiced deaths have occurred during operative procedures. These deaths were presumably due to shock and blood

Received for publication Oct. 23, 1954.

*Abridgment of thesis submitted to the graduate faculty of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Surgery, April, 1954; awarded John Horsley Memorial Prize from the University of Virginia in 1954.

**Markle Scholar in Medical Science.

loss, although it is said that the Greek surgeons sometimes gave their patients narcotic drugs to diminish pain and that occasionally these drugs caused death (Dark, Dinsdale, and associates, 1952).

The first recorded observation on the connection between the circulation of blood and neuromuscular function was by Stenonis in 1667, thirty-nine years after Harvey's demonstration of the circulation of blood. Legallois (1812) is credited with the first statement of a belief in the possibility of resuscitation of parts of an animal or even of a whole animal sometime after death. Hoffa and Ludwig in 1850 demonstrated that electrical stimulation of the mammalian heart causes fibrillation. Steiner (1871) in Billroth's clinic devised a method of *electropunktur* of the heart and was able to resuscitate quiescent hearts of experimental animals but was unsuccessful in resuscitation of a young woman who collapsed under chloroform.

Schiff (1876) stated that dogs killed by chloroform anesthesia could be resuscitated by direct cardiac massage but in no other way. In 1906 Green published a review of the literature on heart massage in cardiac resuscitation and quoted Schiff's statement of 1874: . . . "if the thorax is opened and at the same time air is insufflated into the lungs, by rhythmical compression of the heart with the hand (care being taken in doing so not to interfere with the coronary circulation) and continuous pressure of the abdominal aorta so as to bring the blood in greater quantity toward the head, it was possible to re-establish the heartbeat even up to a period of 11½ minutes after the stoppage of that organ."

A review of the literature relevant to cardiac arrest has been made, and the reader's attention is called to the references.[1-206]

Andrus and Carter (1924) found that rhythm and conduction time in isolated dog's and terrapin's hearts could be correlated with the pH of the perfusate. When an acid perfusate was used, the rhythm slowed and the conduction time lengthened, whereas opposite effects were noted when an alkaline perfusate was employed. Andrus (1924) found that the stimulating effect of sympathomimetic substances (Adrenalin and Tyramine) upon the isolated auricles of the rabbit is enhanced by a pH of 7.8, and diminished by a pH of 7. Conversely, the inhibitory action of vagomimetic substances (acetylcholine and choline) upon the auricle is more pronounced at pH 7 than at pH 7.8.

Brassfield and Gesell (1942) found that stimulation of the peripheral end of the vagus nerve in dogs caused more slowing during hypercapnia than eucapnia. Gesell and associates suggested that "the control of the longevity of acetylcholine deposits by variations in cH may prove to have an important role in neurophysiology" (Gesell and associates, 1942b) and in 1944 showed "potentiation" of humoral intermediation by acid in studies on the turtle heart.

METHODS

Mongrel dogs were anesthetized with sodium pentobarbital, 30 mg. per kilogram of body weight. A tracheal cannula with one-way valves permitted

the dogs to inspire certain gas mixtures and to expire into the room. The right vagus was isolated and divided, and the cardiac end was subjected to faradic stimulation for thirty-five-second periods. At least one minute intervened between successive vagal stimulation periods, and the dogs were equilibrated on each mixture for at least five minutes prior to vagal stimulation. A shielded electrode and either a Harvard inductorium or an Electrodyne stimulator were employed for vagal stimulation. In some instances a No. 10 ureteral catheter was inserted into the right atrium via a foreleg vein, and small amounts of acetylcholine were injected rapidly through the catheter.

Mechanical hyperventilation was induced in some experiments using 20 cm. of water intermittent positive pressure insufflation of the lungs at a rate of 40 to 50 per minute. The gas mixtures used were room air, 10 per cent carbon dioxide with 21 per cent oxygen and 69 per cent nitrogen, 10 per cent carbon dioxide with 10 per cent oxygen and 80 per cent nitrogen, 10 per cent oxygen with 90 per cent nitrogen, and 20 and 30 per cent carbon dioxide with 80 and 70 per cent oxygen.

Blood pH was varied by administration of various carbon dioxide mixtures, hydrochloric acid (0.1N to 1.0N), sodium bicarbonate (0.5 to 1.0N), or mechanical hyperventilation.

Systemic blood pressure was recorded with a femoral artery cannula connected either to a mercury manometer or to a Statham strain gauge and Sanborn multichannel recorder. Electrocardiographic tracings were obtained, and from the blood pressure and electrocardiographic tracings, the duration of cardiac asystole was measured and the heart rate was counted for the first thirty seconds of the thirty-five seconds of vagal stimulation. The time of delay between the injection of acetylcholine and its effect was also obtained from these records.

Acid and basic solutions were injected via ureteral catheters into the ipsilateral femoral vein, and arterial blood samples were drawn from the contralateral femoral artery. Respirations were recorded either with a pneumograph cuff around the thorax or through an intrapleural cannula. Gas analyses were made with the Scholander technique (Scholander, 1942), and arterial blood pH determinations were made under anaerobic conditions at a temperature of 37° C. with a glass electrode (Hemingway and Brown, 1950). Total carbon dioxide content determinations were made on arterial blood with a Van Slyke and Neill manometric apparatus (Van Slyke and Neill, 1924). Carbon dioxide tension, carbonic acid concentration, and bicarbonate concentration were calculated on the basis of arterial blood pH and total carbon dioxide content values, utilizing the Henderson-Hasselbalch equation,

$$pH = pK' + \log \frac{BHCO_3}{H_2CO_3}.$$

The data were studied statistically using the T test for correlated pairs, and the P values (probability of differences between sample statistics arising from errors of random sampling) are given for each comparison.

RESULTS

Sixteen dogs were subjected to hypercapnia, hypercapnia and hypoxia, or hypoxia alone, and under these conditions were subjected to intermittent thirty-five-second periods of faradic stimulation of the vagus nerve. The results of these experiments are shown in Tables I and II. The increase in the effects of vagal stimulation in eleven dogs during hypercapnia are significant as regards the increased bradycardia (P value of 0.001) and the longer period of cardiac asystole (P value of 0.002). Vagal stimulation in ten dogs during inhalation of a gas mixture containing 10 per cent carbon dioxide and 10 per cent oxygen in nitrogen produced significantly more cardio-inhibition than did the same amount of vagal stimulation while these same ten dogs were breathing room air. The P values for the increased degree of bradycardia and the longer cardiac asystole in these ten dogs are 0.002 and 0.013, respectively. Finally, the six dogs that were subjected to vagal stimulation while breathing 10 per cent oxygen in nitrogen did not show an augmentation of vagal stimulation with this degree of hypoxia; in fact, the degree of bradycardia was lessened somewhat (P value of 0.085), whereas the duration of cardiac asystole was unchanged.

TABLE I. EFFECTS OF HYPERCAPNIA, HYPOXIA, AND HYPERCAPNIA PLUS HYPOXIA ON CARDIAC RESPONSE TO VAGAL STIMULATION*

	ROOM AIR	10 PER CENT CO_2	ROOM AIR	ROOM AIR	10 PER CENT CO_2 10 PER CENT O_2	ROOM AIR	ROOM AIR	10 PER CENT O_2	ROOM AIR
Heart rate/min.	107	106	114	138	124	132	119	137	123
Heart beats/30 sec. vagal stimulation	13 ± 1.7	6 ± 1.1	12	15 ± 1.7	8 ± 1.6	15	17 ± 2.1	19 ± 3.0	16
Cardiac asystole, seconds	6 ± 1.3	11 ± 2.2	6	3 ± 0.5	7 ± 1.5	3	2 ± 0.4	3 ± 0.8	2
No. of dogs in each group	11			10			6		

*Values are average values for the number of dogs in each group ± standard error of the mean.

TABLE II. EFFECTS OF HYPERCAPNIA, HYPOXIA, AND HYPERCAPNIA PLUS HYPOXIA ON CARDIAC RESPONSE TO VAGAL STIMULATION*

	ROOM AIR	10 PER CENT CO_2	ROOM AIR	ROOM AIR	10 PER CENT CO_2 10 PER CENT O_2	ROOM AIR	ROOM AIR	10 PER CENT O_2	ROOM AIR
Heart rate/min.	119	116	122	130	116	119	118	136	120
Heart beats/30 sec. vagal stimulation	16 ± 3.0	8 ± 1.6	16	14 ± 2.9	8 ± 2.4	15	16 ± 2.3	18 ± 3.3	15
Cardiac asystole, seconds	2 ± 0.7	5 ± 1.4	2	2 ± 0.6	5 ± 1.5	2	2 ± 0.5	3 ± 1.0	2
No. of dogs in each group		5†			5†			5†	

*Values are average values for the number of dogs in each group ± standard error of the mean.
†Same 5 dogs.

Five of the sixteen dogs were subjected to each of the three gas mixtures; the results of these experiments appear in Table II. Again the effectiveness of vagal stimulation was increased during hypercapnia alone and during hypercapnia plus hypoxia, but heart inhibition following vagal stimulation during hypoxia was unchanged. The P values for the heart rate changes from vagal stimulation during hypercapnia, hypercapnia plus hypoxia, and hypoxia alone,

compared to the values during vagal stimulation while breathing room air, were 0.025, 0.022, and 0.197, respectively. The P values for changes in the duration of cardiac asystole with these same three comparisons were 0.023, 0.052, and 0.058, respectively.

The cardio-inhibitory responses could be repeated many times and were reversible. The reversible effects of 10 per cent carbon dioxide were still present in three dogs which were given intravenous eserine salicylate (0.08 to 0.1 mg. per kilogram of body weight). In fact, the potentiating effect of hypercapnia on vagal-stimulated cardio-inhibition was further enhanced by eserine.

Studies in which blood pH was depressed by administration of carbon dioxide, hydrochloric acid, or lactic acid and others in which blood pH was elevated by mechanical hyperventilation or sodium bicarbonate were also made. In these experiments it was determined which of the variables (blood carbon dioxide tension, bicarbonate level, or blood pH altered by increased carbon dioxide) was responsible for the increased inhibition of the heart produced by vagal stimulation.

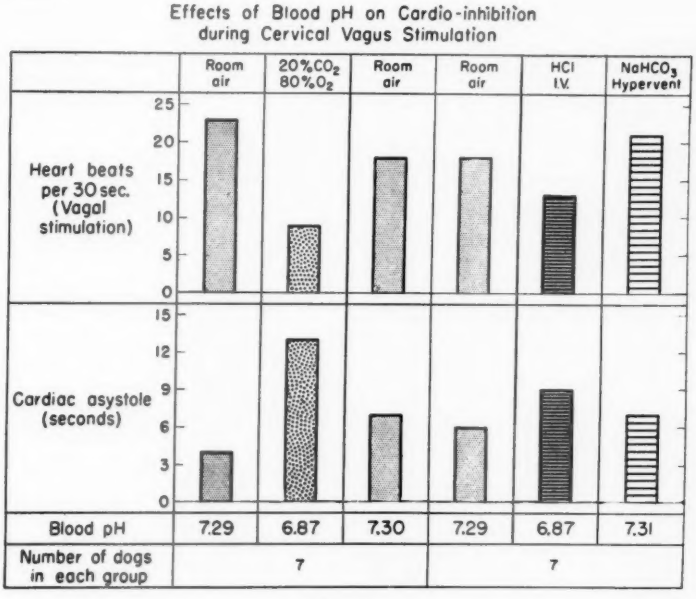

Fig. 1.

TABLE III. EFFECTS OF ACID BLOOD pH ON CARDIO-INHIBITION DURING CERVICAL VAGUS STIMULATION

	ROOM AIR	20 PER CENT CO_2 80 PER CENT O_2	ROOM AIR	ROOM AIR	HCl	$NaHCO_3$ HYPER-VENTILA-TION
Heart rate/min.	155	142	153	169	134	146
Heart beats/30 sec. vagal stimulation	*23 ± 3.2	9 ± 5.0	18	18 ± 5.2	13 ± 5.6	21
Cardiac asystole, seconds	4 ± 1.0	13 ± 3.8	7	6 ± 2.6	9 ± 2.6	7
Blood pH	7.29	6.87	7.30	7.29	6.87	7.31
pCO_2	47	145	45	46	28	32
H_2CO_3	1.4	4.4	1.4	1.4	0.9	0.9
$BHCO_3$	21.5	25.8	20.8	20.6	4.9	14.1
No. of dogs in each group	7			7		

*Mean value ± standard error of the mean.

The effects of lowered blood pH on cardio-inhibition during cervical vagus stimulation appear in Table III and Fig. 1. Inhalation of 20 per cent carbon dioxide in oxygen in seven dogs lowered the blood pH from 7.29 to 6.87 and raised the alveolar carbon dioxide tension from 47 to 145 mm. of mercury. Under the influence of hypercapnia, vagal stimulation significantly increased the degree of bradycardia (P value of 0.005) and the duration of cardiac asystole (P value of 0.049), as compared to the vagal inhibitory effects at the initial pH of 7.29. Intravenous hydrochloric acid in seven dogs lowered the blood pH from 7.29 to 6.87, but the hyperventilation associated with this produced a fall in alveolar carbon dioxide tension from 46 to 28 mm. of mercury. It should be noted that although the falls in blood pH level produced by hydrochloric acid or carbon dioxide are identical, there is a fivefold difference in alveolar carbon dioxide tension under these two conditions. Heart inhibition during vagal stimulation after hydrochloric acid is greater than that in the prehydrochloric acid control period with reference to both the increased bradycardia (P value of 0.024) and the prolonged cardiac asystole (P value of 0.254). Quantitatively, the enhancement of vagal inhibition of the heart is greater with hypercapnia than with hydrochloric acid at the same blood pH level, and a plausible explanation for this apparent discrepancy is a difference in permeability between carbon dioxide and hydrochloric acid. The augmented effects on vagal stimulation associated with carbon dioxide or hydrochloric acid were abolished with the return of the animals to room air or by the intravenous administration of sodium bicarbonate, respectively.

Table IV and Fig. 2 show the results obtained with hyperventilation or with the intravenous administration of sodium bicarbonate. Hyperventilation in six dogs raised the blood pH from 7.26 to 7.70 and lowered the alveolar carbon dioxide tension from 52 to 11 mm. of mercury. Faradic vagal stimulation during hyperventilation produced significantly less cardiac slowing (P value of 0.005) and a shorter period of cardiac asystole (P value of 0.025), as compared to vagal cardio-inhibition at the initial blood pH of 7.26. Intravenous sodium bicarbonate elevated the blood pH from 7.31 to 7.66 in six dogs, but the concomitant depression of respiration raised the alveolar carbon dioxide tension from 51 to 65 mm. of mercury. Whereas the elevation in blood pH with hyperventilation or sodium bicarbonate is similar, that is, 7.70 and 7.66, respectively, the difference in the alveolar tension of carbon dioxide under these circumstances is almost sixfold. However, there is significantly less bradycardia (P value of 0.014) and less cardiac asystole (P value of 0.038) after the sodium bicarbonate administration than there was in the control period at pH 7.31. After hyperventilation was discontinued or carbon dioxide was administered, the respective effects of mechanical hyperventilation and sodium bicarbonate were nullified.

Six dogs breathed 20 to 30 per cent carbon dioxide in 80 to 70 per cent oxygen and the blood pH fell from 7.25 to 6.87 while the tension of carbon dioxide in the alveoli rose from 56 to 162 (Table V and Fig. 3). The bradycardia and cardiac asystole produced by the intravenous injection of small amounts of acetylcholine in animals breathing the carbon dioxide mixture were more pronounced than the heart inhibition effects following the same amounts

of acetylcholine administration to the animals initially when the blood pH was 7.25. There is a significant difference with reference to cardiac slowing (P value of 0.01) and asystole (P value of 0.027). Hydrochloric acid was injected intravenously in six dogs after the cardio-inhibitory effects of acetylcholine had been determined at blood pH 7.28. Hydrochloric acid lowered the pH from 7.28 to 6.90, and the associated respiratory stimulation decreased the alveolar carbon dioxide tension from 55 to 36 mm. of mercury. At comparable blood pH levels, that is, pH 6.87 and pH 6.90, there is greater than a fourfold change

TABLE IV. EFFECTS OF HYPERALKALINE BLOOD PH ON CARDIO-INHIBITION DURING CERVICAL VAGUS STIMULATION

	ROOM AIR	HYPER-VENTILATION	ROOM AIR	ROOM AIR	$NaHCO_3$	20 PER CENT CO_2 80 PER CENT O_2
Heart rate/min.	136	160	138	138	147	132
Heart beats/30 sec. vagal stimulation	*8 ± 0.6	21 ± 2.9	7	12 ± 2.6	25 ± 3.9	12
Cardiac asystole, seconds	10 ± 2.2	4 ± 1.7	13	8 ± 2.6	2 ± 0.5	5
Blood pH	7.26	7.70	7.29	7.31	7.66	7.28
pCO_2	52	11	—	51	65	144
H_2CO_3	1.6	0.3	—	1.5	2.0	4.3
$BHCO_3$	21.3	12.1	—	21.2	68.7	63.9
No. of dogs in each group	6			6		

*Mean value ± standard error of the mean.

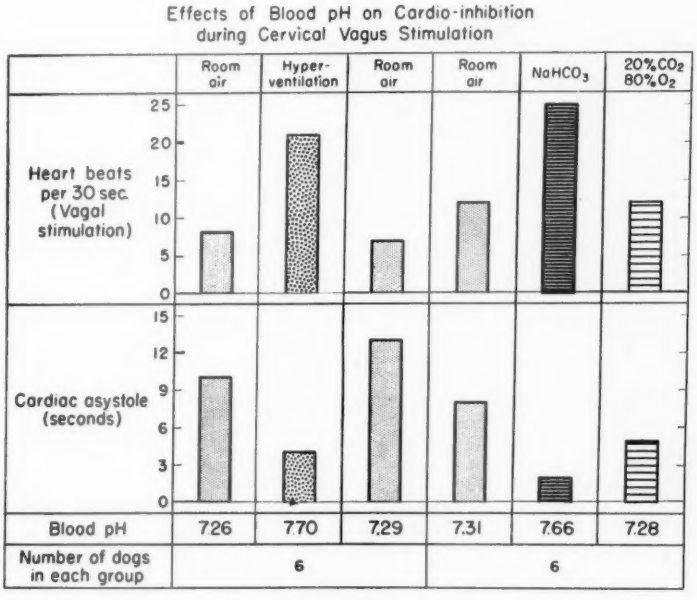

Fig. 2.

in carbon dioxide tension. Again the hydrogen ion concentration seems to be the controlling factor, for the bradycardia and asystole at pH 6.90 are more pronounced than at pH 7.28 (P values are 0.022 and 0.015, respectively). The number of seconds' delay between the injection and response of acetylcholine in the dogs given hydrochloric acid was the same before, during, and after the administration of this acid. However, the delay in the dogs on carbon dioxide

was seven seconds, whereas this value was nine seconds before and after carbon dioxide inhalation. The shorter the delay time, other factors remaining equal, the greater the response to acetylcholine. Consequently, this shortening of delay time further potentiated the enhanced heart inhibition effects of acetylcholine noted with an acid blood pH. Return of the animals to room air or sodium bicarbonate plus hyperventilation abolished the effects of carbon dioxide breathing or hydrochloric acid, respectively.

TABLE V. EFFECTS OF ACID BLOOD pH ON CARDIO-INHIBITION FOLLOWING INTRAVENOUS ACETYLCHOLINE

	ROOM AIR	20-30 PER CENT CO_2 80-70 PER CENT O_2	ROOM AIR	ROOM AIR	HCl	$NaHCO_3$ HYPER-VENTILA-TION
Heart rate/min.	160	142	157	162	129	149
Heart beats/5 sec. during acetylcholine	*5 ± 1.1	1 ± 0.3	5	4 ± 1.2	0 ± 0.1	2
Cardiac asystole, seconds	3 ± 1.7	9 ± 2.6	5	3 ± 0.6	7 ± 1.2	5
Delay in seconds between injection and response of ACH	9	7	9	5	5	5
Blood pH	7.25	6.87	7.23	7.28	6.90	7.40
pCO_2	56	162	—	55	36	35
H_2CO_3	1.7	4.9	—	1.6	1.1	1.0
$BHCO_3$	22.9	28.4	—	21.6	6.3	24.9
No. of dogs in each group	6			6		

*Mean value ± standard error of the mean.

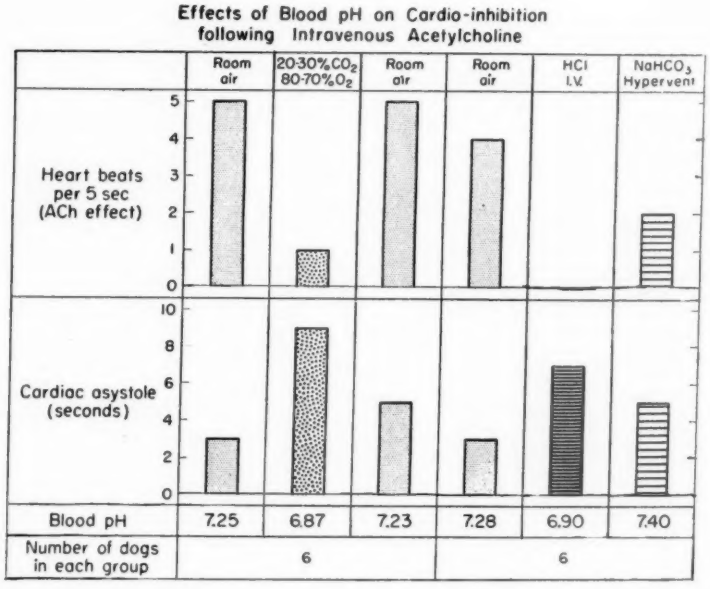

Fig. 3.

The effect of hyperventilation on cardio-inhibition after acetylcholine injections was studied in six dogs (Table VI and Fig. 4). Mechanical hyperventilation in these animals lowered the carbon dioxide tension in the alveoli from 64 to 25 mm. of mercury and the blood pH rose from 7.21 to 7.50. Acetylcholine

injections during the hyperventilation alkalosis produced a shorter cardiac standstill and less bradycardia than the same amounts of acetylcholine had previously when the blood pH was 7.21 (P values of 0.060 and 0.006, respectively). Once more the differences are magnified since the delay time for acetylcholine was longer when the animals were hyperventilated than it was before

TABLE VI. EFFECTS OF HYPERALKALINE BLOOD pH ON CARDIO-INHIBITION FOLLOWING INTRAVENOUS ACETYLCHOLINE

	ROOM AIR	HYPER-VENTILA-TION	ROOM AIR	ROOM AIR	$NaHCO_3$	10-15 PER CENT CO_2 90-85 PER CENT O_2
Heart rate/min.	152	145	140	168	172	143
Heart beats/5 sec. during acetylcholine	*2 ± 0.8	6 ± 1.6	2	2 ± 1.1	1 ± 0.5	0
Cardiac asystole, seconds	6 ± 2.0	3 ± 2.1	6	4 ± 0.7	6 ± 0.6	9
Delay in seconds between injection and response of ACH	8	11	8	6	5	6
Blood pH	7.21	7.50	7.25	7.28	7.60	7.22
pCO_2	64	25	—	47	57	119
H_2CO_3	1.9	0.8	—	1.4	1.7	3.6
$BHCO_3$	24.3	15.7	—	20.2	50.4	45.1
No. of dogs in each group	6			4		

*Mean value ± standard error of the mean.

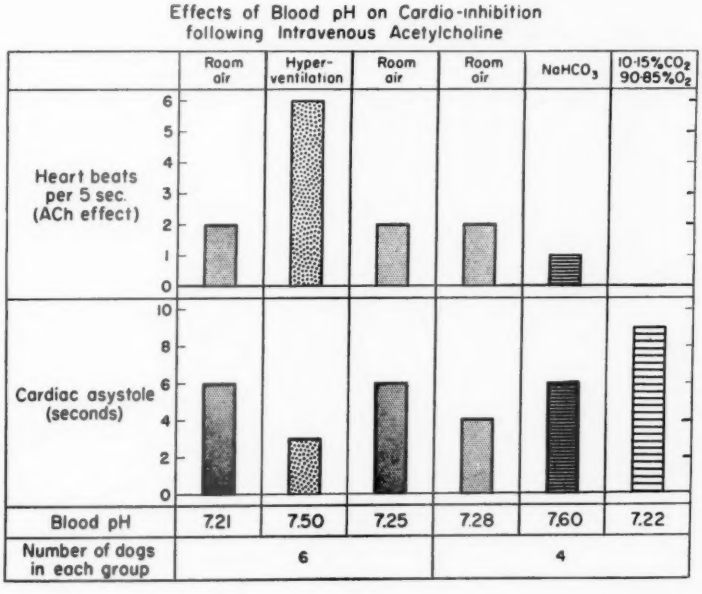

Fig. 4.

or after hyperventilation. Even though a blood pH level of 7.60 was produced in four dogs with sodium bicarbonate, there was no diminution in response to acetylcholine in these animals with respect to either bradycardia or asystole (P values of 0.449 and 0.316, respectively).

DISCUSSION

A potentiation of cardiac inhibition during vagal stimulation was noted in dogs breathing gas mixtures containing 10 per cent carbon dioxide. This is true whether the hypercapnia is associated with hypoxia or not; however, hypoxia per se did not alter the cardiac effects of vagal stimulation.

These results, in general, are in complete agreement with most of the work on isolated heart preparations, but are at variance with some recently reported studies in the intact animals. Sloan (1950) stimulated the intact vagus nerve at the hilum of the lung in thirty-six dogs, and he reported cardiac arrest "only in extreme degrees of oxygen deficiency." However, Sloan's conclusions were based only on terminal findings, at which time the oxygen content of the inspired air was 7 per cent. Sloan included a figure of a typical hypercapnia experiment, in which it is apparent that there is a definite augmentation of cardiac inhibition during vagal stimulation. With no carbon dioxide in the inspired air, the heart was slowed from 172 to 85 beats per minute, whereas the same degree of vagal stimulation slowed the heart from 152 to 40 beats per minute when the concentration of carbon dioxide in inspired air reached 13 per cent. The effects of progressive hypoxia were also illustrated; although potentiation of cardiac inhibition during periodic vagal stimulation was not apparent when the oxygen content of inspired air was 12 to 9 per cent, death occurred when the oxygen content fell to 7.6 per cent.

Young and co-workers (1951) reported that dogs rendered hypercapnic by breathing 20 per cent carbon dioxide mixtures exhibited an enhanced effect of vagal stimulation on the heart. However, they found that hypoxia, even when accompanied by hypercapnia, decreased the cardiac inhibition during vagal stimulation. The results of Grandpierre and associates (1951) and Stewart and co-workers (1953) are in complete agreement with our observations.

It would appear that the alterations in the cardio-inhibitory effects of vagal stimulation in these experiments can be correlated with alterations in blood pH. This general concept applies to heart inhibition following either faradic stimulation of the cervical vagus or the intracardiac injection of acetylcholine.

These data can best be interpreted in the light of the optimum pH range for cholinesterase activity. Augustinsson (1948) quoted the figures of many physical chemists who state that the optimum pH range for cholinesterase activity is pH 7.5 to 8.5. Consequently, in the presence of an elevated blood pH, cholinesterase should be more effective in inhibiting acetylcholine (either endogenous acetylcholine released by vagal stimulation or exogenous injected acetylcholine) than it would be at a normal blood pH. In the presence of an elevated blood pH, therefore, the cardio-inhibitory effects of vagal stimulation or acetylcholine should be decreased. Conversely, as the blood pH is decreased with carbon dioxide, or hydrochloric acid, or lactic acid, the acetylcholine is less rapidly hydrolyzed by cholinesterase than it was at a normal blood pH. Subsequently, cardio-inhibitory effects are enhanced in the presence of an acid blood pH.

During vagal stimulation the endogenous release and cardio-inhibitory effect of acetylcholine are dependent on blood pH and particularly the cellular

pH of the effector organ, in this case the heart. The pH measurements in the study were made on arterial blood, and critical values for intracellular hydrogen ion concentration in the heart are not known. One may assume a qualitative relationship but evidence for quantitative differences are real.

Jacobs (1920a) found that flowers of *Symphytum peregrinum* contain a natural indicator sensitive to carbonic acid, which may be used to study cell penetration by carbon dioxide. Jacobs reported that a condition of intracellular acidity can be produced by a slightly alkaline solution of carbon dioxide in sodium bicarbonate almost as effectively as by a solution of carbon dioxide in distilled water, although the hydrogen ion concentration of the latter solution is approximately 4,000 times as great as that of the former. The hydrogen ion concentration of a carbonated solution was not the most important factor in determining its toxicity for tadpoles, since the same hydrogen ion concentration produced by hydrochloric acid was "incomparably less effective" (Jacobs, 1920b). Smith in 1926 studied the action of various acids on excised atrial tissue from a turtle and found this tissue freely permeable to carbon dioxide. From experiments with hydrochloric and lactic acid, Smith concluded that the hydrogen ion penetrates the atrial tissue, provided a sufficient concentration difference between fluid and cell is established; and that the final equilibrium is characterized by a considerable difference in the hydrogen ion concentration in fluid and cell. In studies on the influence of hydrogen ion concentration upon the heart volume in dogs, Gremels and Starling (1926) found that at the same pH change carbon dioxide produced a greater effect than HCl, due to the greater penetrating power of carbon dioxide.

In summary, one would expect to find, at the same acid blood pH level, greater cardio-inhibition from vagal stimulation following hypercapnia than following hydrochloric acid administration, due to the greater cellular permeability of carbon dioxide. This is precisely what was found, as demonstrated in Table III and Fig. 1.

Quantitatively the decreased effects of faradic vagal cardio-inhibition at hyperalkaline blood pH levels are similar, whether the blood is made more alkaline by either hyperventilation or sodium bicarbonate, Table IV and Fig. 2. Relevant to this similarity, perhaps, is Smith's (1926) observation that atrial tissue is "apparently permeable to the bicarbonate ion."

Injected (exogenous) acetylcholine is hydrolyzed to a varying degree by the cholinesterase in the blood, prior to acetylcholine's arrival at the "effector" organ. The amount of acetylcholine hydrolysis en route to the "effector" varies with blood pH and specific ionic effects, and the effectiveness of acetylcholine at the effector organ is probably dependent on cellular pH. Indirect evidence for the major role played by acetylcholine hydrolysis in the blood is the quantitative similarity of cardio-inhibition following acetylcholine in dogs subjected to carbon dioxide inhalation and hydrochloric acid, Table V and Fig. 3. This is true in spite of known cellular permeability differences between carbon dioxide and hydrochloric acid referred to earlier.

The correlation between pH and cardio-inhibition is again noted in the hyperventilated dogs which were given acetylcholine, but there is no correlation

between pH and acetylcholine inhibition of the heart following sodium bicarbonate, Table VI and Fig. 4. A possible factor in this apparent discrepancy is an alteration in the ratio of sodium to potassium in the cardiac nodal tissue during acetylcholine administration (Obrink and Essex, 1953). The increased sodium following the intravenous injection of sodium bicarbonate would tend to prolong the sensitivity of the nodal tissue to acetylcholine. Another factor is cholinesterase inhibition by the sodium ion (Myers, 1952), but the earlier experiments of Glick (1941) do not support this view.

Miscellaneous observations made during this study include the rather marked variabilitiy in the amount of hydrochloric acid, lactic acid, and sodium bicarbonate necessary to produce the same pH change in different dogs. This observation, as well as the finding of an occasional sudden death during the rapid, initial administration of sodium bicarbonate, was previously made by Terroux and associates (1947). A nicotine-like action as well as the muscarine action of acetylcholine was also observed.

Laboratory evidence for potentiation of cardio-inhibitory effects during chemical and faradic vagal stimulation should have a direct bearing on the same problem in clinical surgery. Because vagal stimulation is inadvertently produced at the time of endotracheal intubation or extubation, when the patient is somewhat light and reflexes are less depressed, the occasional cardiac arrests encountered at such times are probably more than coincidental. In fact, Shumacker and Hampton (1951) reported five deaths in patients with cardiac disease simultaneously with aspiration through or removal of an endotracheal tube.

Furthermore, operative manipulation by the surgeon (in the thorax or abdomen) inadvertently causes a varying degree of vagal stimulation, especially along the afferent pathways. The trauma incident to surgical procedures is usually innocuous as far as cardio-inhibitory effects are concerned, but under conditions of an acid blood pH the potentiation of such reflexes may prove fatal. Although it is true that adequate preoperative medication and the judicious use of procaine and atropine supplementation during surgery will tend to block such reflexes, the importance of preventing carbon dioxide accumulation should be reiterated. Through the years the need for adequate oxygenation of the surgical patient has attained a role of paramount importance in surgery and anesthesiology; an unfortunate by-product of such emphasis has been relative neglect of carbon dioxide accumulation. Relevant to potentiation of vagal reflexes, however, hypercapnia and not hypoxia plays the more major role. Moreover, the mechanism of this augmentation, as judged by the data in this thesis, is the decreased hydrolysis of acetylcholine in the presence of an acid blood pH. Again it should be noted that under conditions of acidosis respiratory, metabolic, or combinations thereof), the response of the heart to sympathetic stimulation is depressed while the response of the heart to vagal stimulation is enhanced.

Whereas Deming (1952) stressed the relatively large oxygen consumption and the insidious onset of hypoxia in infants and young children (in spite of

an oxygen content in the anesthetic mixture deemed adequate), it is only reasonable to deduce that the danger of carbon dioxide accumulation in these patients is omnipresent and connotes a definite relationship between the difficulties with respiratory management and the frequency of cardiac arrest in children. Stephenson and co-workers found that 21 per cent of the 1,200 cases of cardiac arrest which they collected were in children under 10 years of age (Stephenson and co-workers, 1953).

In most discussions of cardiac arrest, treatment monopolizes the words, and probably thoughts, of participants. The "new" approach to direct cardiac massage voiced in the recent surgical literature appeared in the European literature prior to 1900. Although recent papers have been instrumental in the dissemination of knowledge relevant to treatment of cardiac arrest, one should not lose sight of the fact that prophylactic rather than therapeutic measures produce the larger yield.

Investigations reported herein do not explain "the" cause of cardiac arrest, but perhaps they cast a certain amount of old and new light upon a portion of the problem.

Many surgeons and anesthesiologists have noted the improved cardiac tone and increased cardiac rate associated with the active "bagging" of patients undergoing intrapleural surgery, especially when the lungs had previously been inadequately ventilated. The improved cardiac status is probably due, in part, to correction of the patient's hypercapnia and not due solely to the correction of hypoxia.

SUMMARY AND CONCLUSIONS

In the initial portion of the study, dogs were subjected to hypercapnia, hypercapnia and hypoxia, or hypoxia alone. Hypercapnia alone or hypercapnia plus hypoxia augmented the cardiac inhibition during faradic vagal stimulation. Hypoxia did not increase the effect of vagal stimulation; in fact, it may have lessened it.

With this background, studies in which blood pH was depressed by administration of carbon dioxide, hydrochloric acid, or lactic acid and others in which it was elevated by mechanical hyperventilation or sodium bicarbonate were also made. In these experiments it was determined which of the variables (blood carbon dioxide tension, bicarbonate level, or blood pH) altered by increased carbon dioxide was responsible for the increased cardiac inhibition produced by faradic vagal stimulation or acetylcholine injection. In general, the alteration in the cardio-inhibitory effects of either faradic vagal stimulation or acetylcholine observed in these experiments can be correlated with changes in blood pH. The well-documented observation of optimum cholinesterase activity between pH 7.5 and 8.5 is used in the interpretation of the results. In addition to cholinesterase activity, differences in cellular permeability between the various substances used to alter blood pH are discussed with reference to these experiments.

Because of the definite augmentation in cardiac inhibition in the presence of an acid blood pH, it would seem important to avoid or correct such a state in surgical patients. Possibly the avoidance of acidosis during operative procedures will decrease the incidence of cardiac arrest.

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Appraisal of Progress in Surgical Therapy

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FLUID AND ELECTROLYTE BALANCE IN THE IMMEDIATE POSTOPERATIVE PERIOD

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ANY consideration of fluid and electrolyte balance in the immediate postsurgical period is incomplete without an examination of the preoperative and operative factors existent in the individual patient coming to surgery. Whenever even slightly indicated, preoperative electrolyte determinations should be made, and immediate correction of potassium, sodium, or chloride deficiencies are now basic tenets of modern care. These factors all become increasingly important as the age of the average patient undergoing major surgery increases, a careful study of the whole preoperative nutritive status being especially needed in the older age group. Concealed but very real protein deficiencies may hide securely behind a sketchily obtained history of the patient's recent dietary habits. As emphasized by Cole,[1] an acute weight loss of 5 to 6 pounds has much greater significance than a loss of 25 pounds over a period of months. An estimation of the plasma proteins may help unmask a protein deficiency, which on correction would undoubtedly spare the patient an increased susceptibility to the ill effects of anesthetic agents and blood loss, delayed wound healing, delayed functioning of gastrointestinal stomas, and delayed callus formation. Somewhat less definite but equally important to avoid by better nutrition is a long, drawn-out convalescence, with prolonged weakness, lassitude, and failure to gain strength and vigor in a reasonable period of time. A total plasma protein level of 5.5 Gm. is accepted as the critical level for edema formation,[2] but edema can occur with much higher figures, and the point of edema formation is far too low an indicator of a satisfactory, nutritive state for surgical patients. It is important that the so-called "labile protein," which is that stored protein which can be quickly converted into plasma protein in the event of emergency need, be present in peak amounts before an operation. Food by mouth is the most nourishing, and Cole has emphasized the value of a gain of even three to five pounds in weight as an indication of improved nutrition. Studies have shown protein hydrolysates to be 70 to 100 per cent utilized in building up lowered protein reserves, provided the caloric requirements are covered.

Received for publication July 12, 1955.

With few exceptions, the period of operation is not a desirable time to attempt correction of water and electrolyte deficits, since, fundamentally, the kidneys are not working during operations. The immediate postoperative time is also a period of disturbed kidney function. In a series of experiments involving the diuretic response of postsurgical patients to rapidly administered infusions of 5 per cent dextrose in water, Cooper, Iob, and Coller[3] noted that the usual initial diuresis was lacking and that during this oliguric period, ranging from six to twelve hours postoperatively, there was a minimal output of sodium and chloride, with a positive load of water. On this basis, it was recommended that intravenous infusions during the operation and for twelve hours after surgery be limited merely to replacement of blood loss plus a sufficient quantity of 5 per cent glucose in water to cover insensible losses. This insensible vaporization will, of course, vary with such conditions as fever, hot, humid climates, number and weight of drapes, and so on, but for practical purposes it may be expressed as approximately 200 ml. per hour. In any event, unless uncorrected electrolyte deficits are still present during surgery, the distressing, ever-present flask of saline solution running into the patient during surgery should be dispensed with.

In recent years, the postoperative period has been extensively studied, and numerous investigators, notably Ravdin,[4] Coller,[3] Moyer,[5] Moore,[6, 7] and Elman,[8, 10] have thrown much light on many poorly delineated and imperfectly understood factors concerned with the reaction of the human organism to trauma and surgery. As a result, it may be seen that, despite individual variations as to type of operation, disease, or age, the postoperative surgical patient follows a certain general pattern of response which is modified to a variable degree by the extensiveness of the trauma, preoperative depletion by illness, starvation, previous trauma or operation, functional capacity of the adrenals, and the presence and amount of extrarenal loss of water, crystalloids, and protein. These changes may be briefly stated as follows.

1. A slight elevation of temperature and pulse rate. This temperature elevation of one or two degrees is due perhaps to an interference with heat loss and, partly, to a change in the central control of sweating with decreased perspiratory volume. Ionic perspiratory changes are similar to those observed in the urine.

2. A decrease in urine excretion, which is usually transient in the immediate postoperative period and accompanied by a decreased excretion of sodium for two to five days, followed by sodium diuresis. Along with this decrease in sodium excretion, there is also a decreased excretion of urinary chlorides. The water retention is considered to be the result of activation of the hypothalamiconeurohypophyseal mechanism with release of antidiuretic hormone. The sodium retention is believed to be a manifestation of concurrent activation of the adenohypophyseal-adrenocortical mechanism with subsequent increased adrenocortical activity, as evidenced by an increased

urinary excretion of adrenocorticoids and a variable drop in the circulating eosinophils. Recent investigations revealed that some of the sodium retention is due to sodium deposition in traumatized tissue.

3. A moderate loss of potassium in the urine for two to five days, followed by potassium retention. The urinary potassium excretion begins during the surgical procedure, increases markedly in the first twelve to fifteen hours postoperatively, and continues at a high level through the next day. Usually the excretory curve drops during the subsequent two to three days and is followed by extremely low rates of excretion and later retention. The kidney during trauma has little ability to conserve potassium, with losses up to 50 per cent of that given being recorded. There is usually little or no change in plasma potassium concentration during this period.

These potassium losses are thought to be due to the interaction of several important mechanisms, namely, increased tissue catabolism, possibly dehydration, and the influence of the adrenal cortical hormones. Studies on potassium concentration in biopsies of traumatized muscle taken from operative sites revealed that the damaged muscle lost up to 55 per cent of its potassium within four to five hours. The losses tended to parallel the degree and extent of trauma.[7] The potassium losses are greater than can be accounted for by loss of protein alone.[7] In the event of extracellular dehydration for any reason, vomitus, gastrointestinal suction, and so on, potassium passes out of the cell with the intercellular water in an attempt to restore the depleted interstitial space. With the administration of fluids to correct the dehydration, a diuresis is provoked with subsequent large renal losses of potassium, due to the inherent inability of the kidney to retain potassium.

4. A loss of nitrogen from the body for a variable period, usually three to seven days.[7] This period of negative nitrogen balance is normally accompanied by a period of starvation and relative caloric deficiency. With the resumption of an adequate intake of nitrogen and calories, a positive nitrogen balance usually ensues. It should not need to be emphasized that for recovery to occur the patient must come into a positive nitrogen balance.

5. An increase in the extracellular fluid volume and a concomitant decrease in the intracellular fluid volume. These changes are probably due, in part at least, to variations in permeability of the cell membrane, perhaps effected by the adrenocorticoids.

In addition, gastrointestinal secretion is decreased with increased adrenocortical activity, and urinary creatinine excretion is increased after surgery, probably as a result of increased metabolic activity of the whole body muscle mass.

From the foregoing aggregate of facts, several clinical correlations have been postulated which are of far-reaching significance in the maintenance of postoperative fluid and electrolyte balance.

As stated previously, during the operative procedure excessive administration of fluids is to be avoided, since antidiuretic hormone is released in effective amounts even during the anesthetization of the patient. Only enough

fluid, in addition to replacement of whole blood, necessary to provide corrections for the insensible losses is needed or advisable during the operation and the first twelve hours after operation. Often in the operating room the surgeon's attention is taken up with the technique of the operation itself and the anesthetist manages the intravenous fluids. Without some plan arrived at beforehand, or without watching carefully, too much fluid will be given and the twenty-four-hour total may easily be 3 L. or more. With the water retention of this period, the urine output often is generally not more than 500 to 700 ml., and overhydration occurs. In the same way, 3,000 or more ml. of fluid may be given on the first and second postoperative days, which, with continued water retention, adds to the overhydration. When marked, disturbing hypoproteinemia develops and the symptoms and signs of water intoxication occur. On the third or fourth day the water retention phase begins to pass and one then sees a urinary diuresis of 2,000 to 4,000 ml. daily, which is far too much. The total daily fluid intake during this early period should seldom be more than 2,000 ml.

Knowledge of water retention during the operative and immediate postoperative periods should prevent the surgeon from trying to obtain a urine output of 1,000 or more ml. per day by "pushing fluids." It will not work at this time and will do harm by overhydrating the patient.

The kind of fluid to rely upon mainly during the operative and immediate postoperative period is 5 to 10 per cent dextrose in water. Two liters of this will, in a comfortable environment and for patients without much fever and no hyperthyroidism, provide enough water for a day's vaporization and urine. One hundred grams of glucose is sufficient to prevent ketosis and exerts the maximum sparing effect on protein destruction. Greater amounts will not accomplish more in this regard.

Because of the decreased excretion of sodium and chloride during the operative period and for one or two days postoperatively, salt solution should be given sparingly or only when specially indicated during this time. Moore recommended that salt solutions be withheld until after the fifth postoperative day, if there is no abnormal extrarenal sodium loss. Coller and associates,[5] noting that the postsurgical kidney could not concentrate salt in a normal fashion, recommended that a hypotonic solution containing 0.45 per cent NaCl or 0.38 per cent NaCl and 0.11 per cent $NaHCO_3$ be used in place of normal saline after the early phase of salt retention had passed. Winfield, Fox, and Mersheimer,[9] recounting the unphysiologic nature of the so-called "physiologic or normal saline," pointed out that the latter contains 50 per cent more chloride than does plasma, and they recommended a solution containing Na, Cl, Ca, and Mg ions in a concentration similar to plasma. Their solution also takes note of the increased potassium loss during the postoperative period, and contains twice the plasma concentration of potassium. In addition, since acetate accelerates renal transport mechanism and is rapidly converted into bicarbonate, it also is included in the solution. Administration of this solution in amounts up to 1 L. on the day of operation and 2 to 3 L. on succeeding

postoperative days resulted in urine volumes which averaged over 1 L. the day of operation and ranged around 1,500 ml. for the next four postoperative days, a sodium excretion of 188 meq. the day of operation and over 200 meq. for the following days, and a chloride excretion of 160 meq. the day of operation and over 170 meq. the following days. During this period these examiners noted essentially normal plasma levels of K, HCO_3, Na, and Cl.

Elman and Weichselbaum[8] recommended, for the postoperative patient uncomplicated by abnormal losses from the skin, gastrointestinal tract, or urine, a simple electrolyte mixture containing 34 meq. Na, 33 meq. K, 34 meq. Cl, and 18 meq. P, given in 2 L. of fluid, which may be either 10 per cent glucose in water or a 5 per cent glucose–5 per cent amino acid mixture. With this solution they noted only a slight sodium retention in contrast with the marked retention previously noted by others.

Replacement of the urinary potassium losses in the immediate postoperative period is rarely necessary or desirable. This excretion is part of the body's natural response to stress and during the first three days after surgery will range between 80 and 120 meq. By this time most patients are usually eating and drinking and there is no problem, since most foods contain enough of this salt. Should parenteral therapy be needed after the fourth or fifth day, then KCl should be given, along with Na and Cl, in amounts up to 80 meq. per day. Usually not more than 40 meq. are added to a liter of intravenous fluid. One should always remember to give no potassium if oliguria is present, since, with poor kidney function, a possibly fatal hyperkalemic state might develop.

We have not dealt with the problem of abnormal losses of water and electrolytes in the immediate postoperative period, since this article is concerned primarily with the metabolic effect of trauma in water and electrolytes, and what to do about it. Such abnormal losses, however, are common among general surgical patients because of the frequent use of continuous gastrointestinal suction. Briefly, replacement is not difficult when one records the daily amount drained, considers the average ionic concentration of the fluid aspirated and administers volume for volume a suitable electrolyte fluid, and depends upon the kidneys to aid the balance by saving some ions and excreting others.

CONCLUSIONS

With the best of experimental evidence at hand today, the immediate postoperative period calls for only moderate amounts of fluid and no electrolytes unless abnormal extrarenal losses are occurring.

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